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PREFACE

The favorable reception accorded to the first volume of papers from the medical department of the Graduate School of the University of Minnesota warrants the publication of a second volume, containing the papers accumulated from July 1, 1920 to July 1, 1922. The publication of these papers enables the general medical profession readily to keep in touch with the clinical and experimental studies in the medical department of at least one graduate school. Many of these studies, it is believed, are of wide general interest. Others in narrower lines later may prove to be of fundamental importance. It is important that this material should be placed before the medical profession as briefly as is consistent with clearness and accuracy. Many of the articles, therefore, have been greatly abridged and others are presented in abstract. Nearly all of them were originally in the form of theses presented by graduate medical students of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science or Doctor of Philosophy. There are also a few papers, other than theses by the graduate medical students, and a few on medical education by members of the graduate faculty. The experimental studies have been made in the laboratories of the Medical School and the Mayo Foundation of the University of Minnesota. The clinical studies have been made in the University Hospital, in other hospitals in Minneapolis and St. Paul controlled by the Medical School, and on the clinical material in the Mayo Clinic which is available for study by graduate medical students in the Mayo Foundation. All the articles have been passed on by the publication committee with the assistance of other members of the faculty.

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I

ALIMENTARY TRACT

DEVELOPMENT OF THE MUSCULATURE OF THE STOMACH WITH SPECIAL REFERENCE TO ITS CONDITION IN THE NEWBORN CHILD AND THE PREMATURE INFANT*

ELWYN H. WELCH

The structure and architecture of the muscular coat of the adult stomach of man is well known, as the result of numerous researches in which a variety of procedures and technics have been employed. This knowledge of the structure of the organ has been well correlated, as a whole, with its motor functions through studies by means of roentgenographic and other physiologic technics. However, we have almost no precise information with regard to the development of the muscle architecture of the stomach and its condition at birth and during infancy. Most of the observations on the embryology of the gastric musculature are in scattered notes or statements incidental to studies on other phases of the stomach; while our knowledge of its condition in the newborn seems to be represented by a few statements in older literature on pediatrics. The study was undertaken with the hope of determining the history of the gastric musculature in the embryo and the fetus, and its condition in the newborn and young infant.

MATERIAL AND METHODS

The data which form the basis of this paper have been derived from the study of serial sections of human embryos from glycerin preparations and microscopic dissection of thirteen fetal stomachs, and ten stomachs of the newborn and neonatal period. The sectioned material from the collection in the Anatomical Laboratory of the University of Minnesota, includes a well distributed series of embryos from 5 to 158

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* Abridgment of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Arts, 1922. From the Department of Anatomy, under the direction of Dr. Richard E. Scammon, University of Minnesota, Minneapolis.

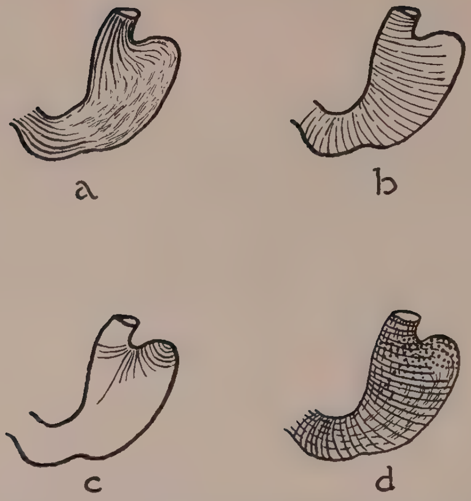

Fig. 1.—Anterior surface of the cleared and dissected stomach of an embryo 61 mm. in crown-rump length. (× 1⅓.) a. Longitudinal layer. b. Circular layer. c. Oblique and circular fibers of the fundus. d. Longitudinal and circular layers, and oblique and circular fibers of the fundus.

(Note: The above explanation of the different muscular layers of the stomach, designated a, b, c, and d, applies to all figures from 1 to 14.)

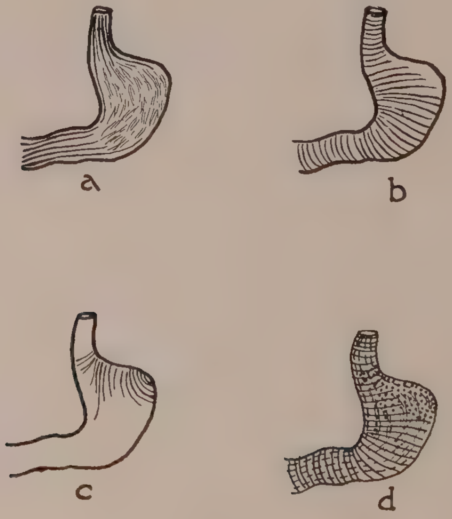

Fig. 2.—64 mm. (× 1⅓.)

Figs. 2 to 10 are cleared and dissected stomachs from embryos of the following crown-rump lengths.

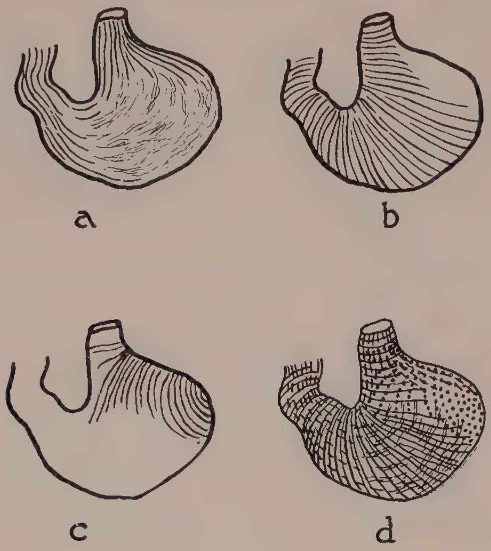

Fig. 3.—65 mm. (× 1⅓.)

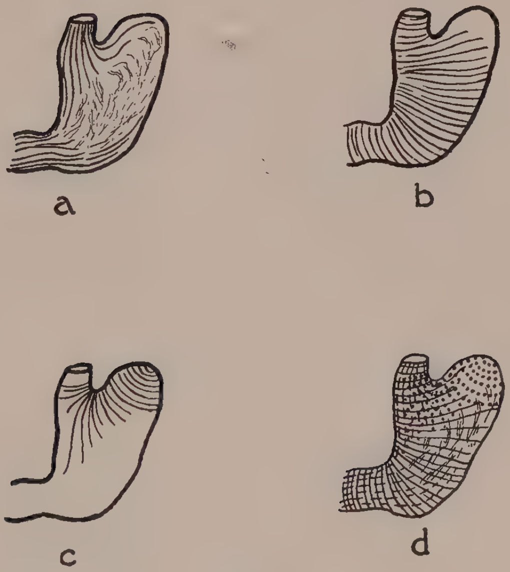

Fig. 4.—95 mm. (× 1⅓.)

mm., crown-rump length. Fetal stomachs, studied grossly, were from fetuses of 61 to 175 mm., crown-rump length. A series of dissections were also made of stomachs of infants from three to ten months of age.

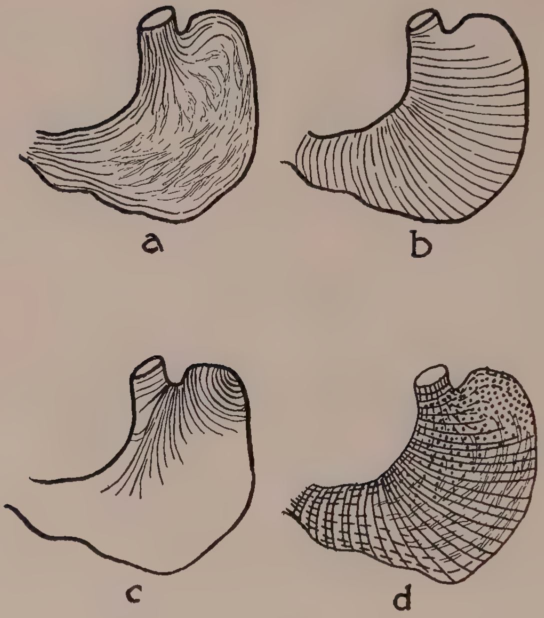

Fig. 5.—107 mm. (× 1⅓.)

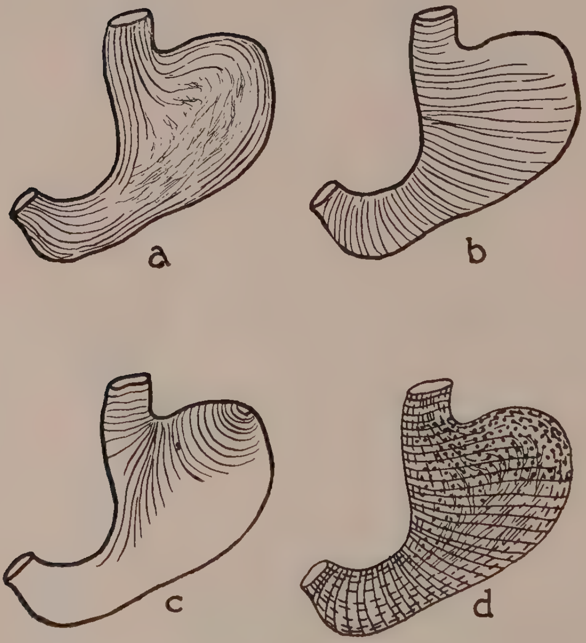

Fig. 6.—114 mm. (× 1⅓.)

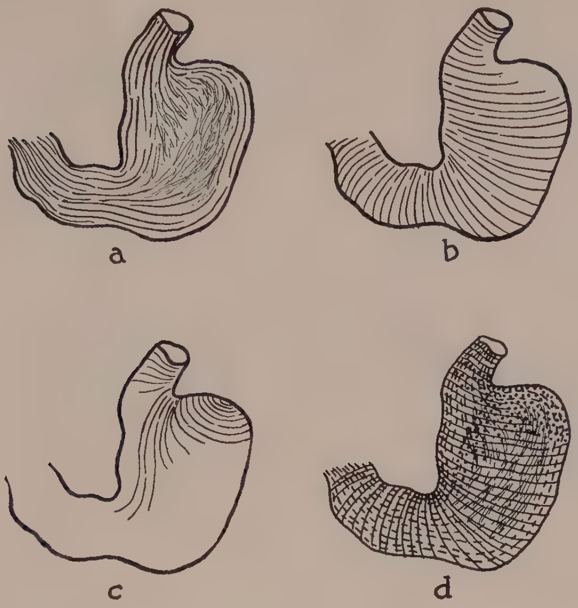

FIG. 7.—129 mm. (× 1.)

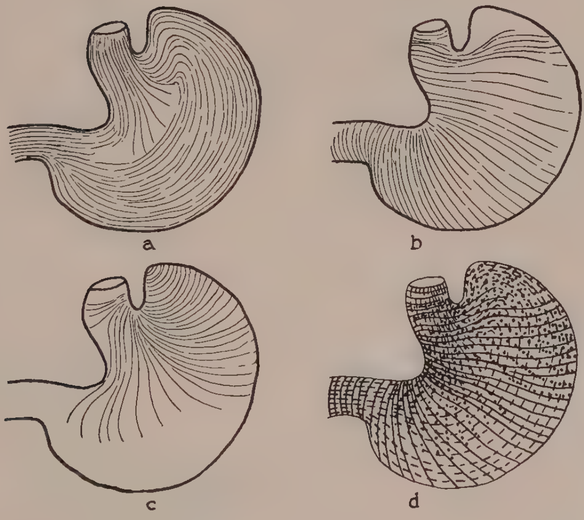

FIG. 8.—148 mm. (× 1.)

The glycerin preparations were first opened, the mucosa carefully removed by scraping and the specimens placed in borax carmin for twelve hours. They were immersed in a half glycerin, half water mix-

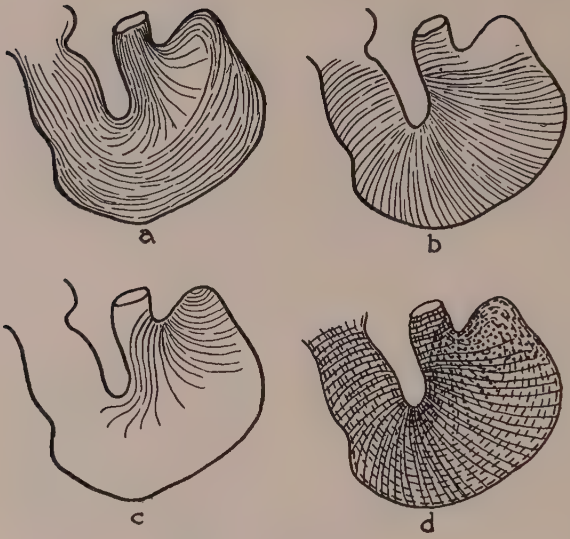

FIG. 9.—165 mm. (× 1.)

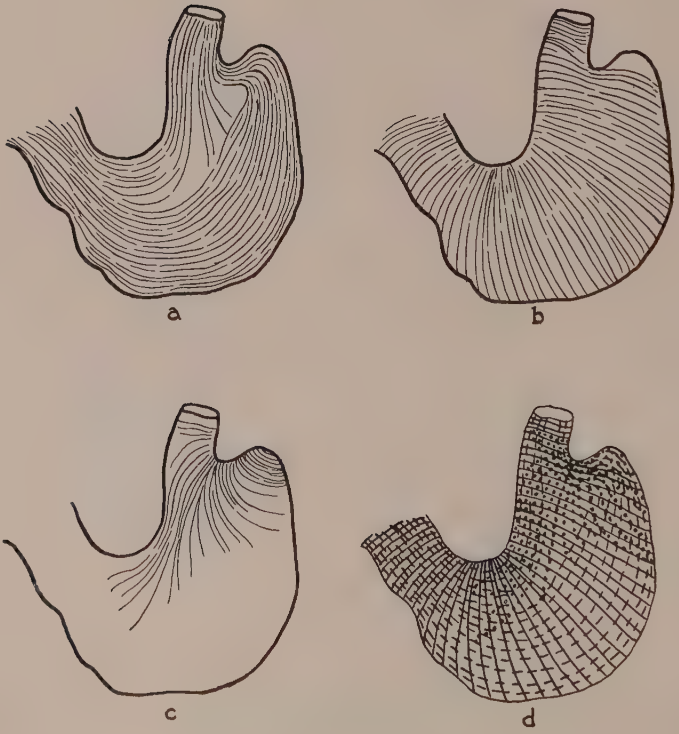

FIG. 10.—175 mm. (× 1.)

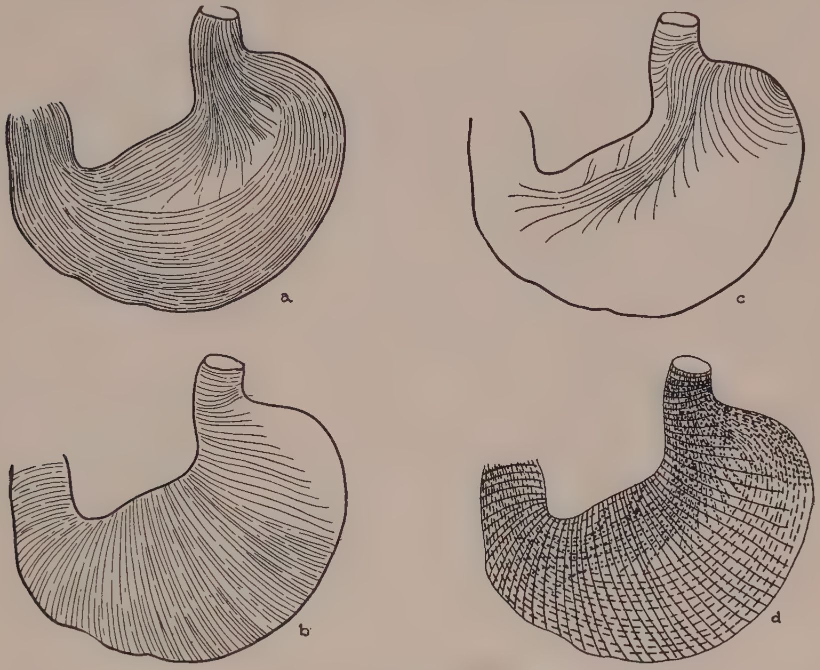

FIG. 11.

FIGS. 11 to 14.—Stomachs of newborn; dissected after clearing in glycerin. (× 4/5.)

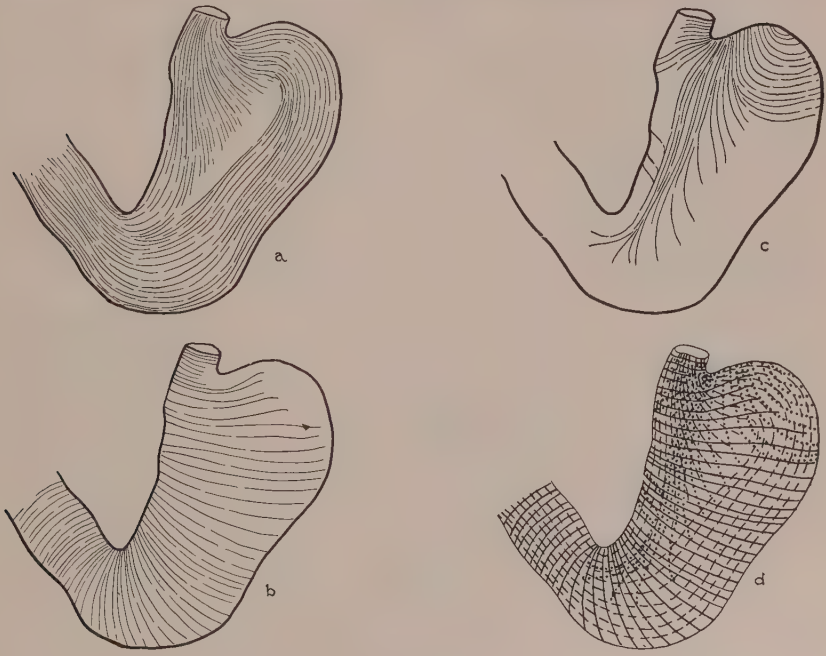

FIG. 12.

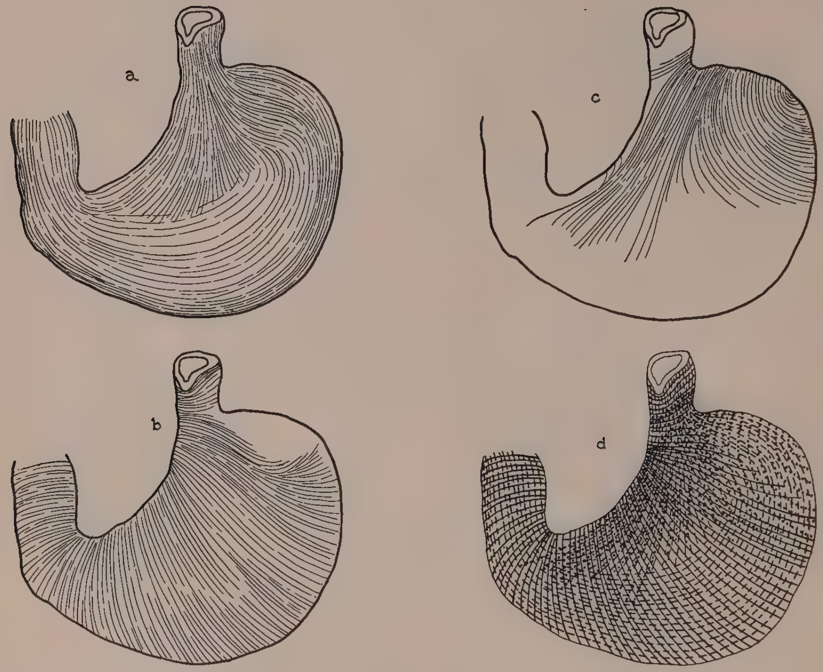

FIG. 13.

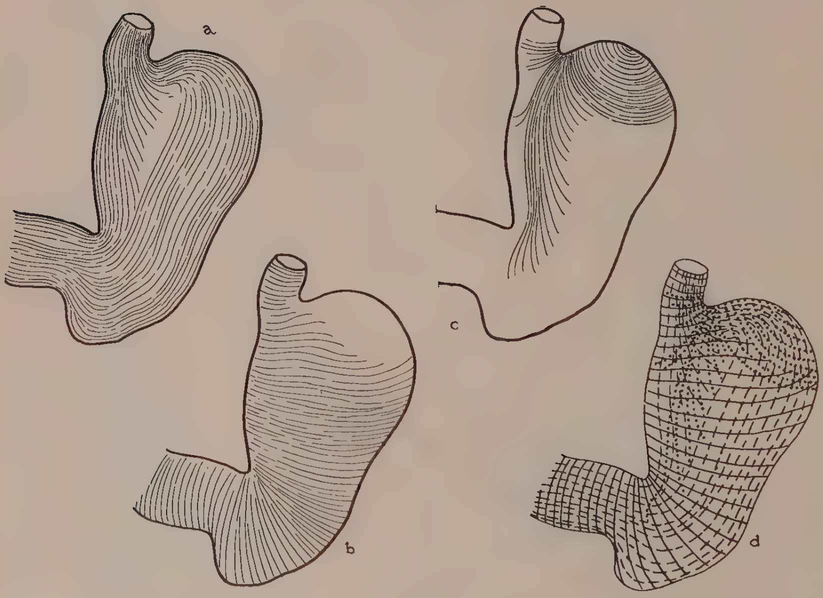

FIG. 14.

ture until thoroughly saturated, carried through dilutions of two parts glycerin and one part water, and three parts glycerin and one part water, to pure glycerin. When spread on a glass plate on the binocular or microscope stage and illuminated from below by a fairly strong light, material prepared in this manner showed the individual muscle bundles very clearly.

In order to facilitate microscopic dissection, all of the stomachs thus studied were placed in a solution of 5 per cent nitric acid in 70 per cent alcohol to loosen the connective tissue. Afterward they were moderately distended with either gelatin or plaster of Paris. The muscle layers were then explored with extremely fine points and forceps, traced in their course and relations, and finally removed, a bundle at a time. This method is somewhat laborious and tedious, but it has advantages over other methods for certain phases of the work. Of the two distension mediums, plaster of Paris is decidedly the more satisfactory, mainly because of its permanency. Any injury to the mucosa through the circular muscle layer readily permits effusion of the gelatin and consequently deflation of the organ, making this filler highly inconvenient.

LITERATURE ON THE DEVELOPMENT OF THE MUSCULATURE OF THE STOMACH

Very little is known of the early formation of the muscular layers of the stomach. Lewis described the development of the outer layers of the stomach beginning with a 10 mm. embryo. At this stage the three layers composing the gastric wall are entodermal epithelium, mesenchyma, and peritoneal epithelium. The circular portion is the earliest of the muscle layers to appear and is first differentiated by a condensed zone of the mesenchyma in embryos of 16 mm. While it can be identified over the greater portion of the stomach, it is best defined along the lesser curvature. According to Broman, Tandler has described this stage at 13 mm. Completion of the circular layer with the appearance of a tunica propria characterizes embryos of 22.8 mm. This stage also shows a slight thickening toward the pylorus, while a prolonged gradual thickening, followed by an abrupt thinning at the duodenum is demonstrable at 37 mm. and in all subsequent stages.

The first "inner longitudinal" bundles appear in the region of the cardia and fundus in 91 mm. embryos.[8] The first mention of such fibers by Giannelli and Lampronti is in a fetus of five months. At this stage at the level of the pylorus one can see running in the circular layer "les petits faisceaux des cellules musculaires lisses obliques" of which some reach almost to the submucosa. "Ces petits faisceaux *ne sont pas en continuité* avec les fibres de la couche musculaire longitudinale."

At 120 mm. Lewis has followed the longitudinal layer of the esophagus for a short distance over the cardia external to the circular layer. However, at this stage the greater portion of the stomach has only the circular layer. In the region of the pylorus there is a distinct outer longitudinal layer at 240 mm. which is much thickened toward the duodenum. Some of its fibers are described as being continuous with the more superficial layer of the duodenum, while the deeper fasciculi appear to turn into the thick circular layer near the pylorus to form the "dilator pylori" described by Cunningham.

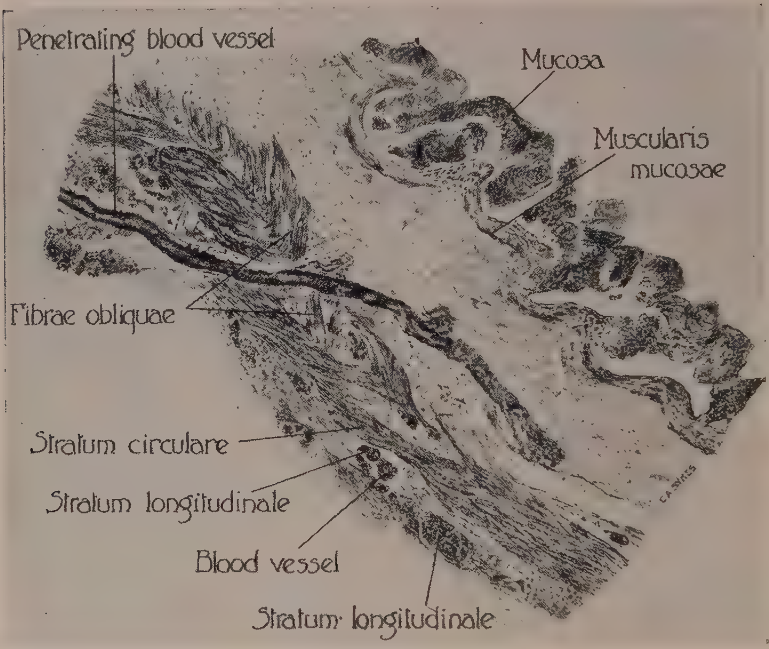

FIG. 15.—Section through mid-ventral wall of the stomach in the region of the cardia. From an embryo of 65 mm. crown-rump length. (× 130.)

Taguchi studied two embryos, one 144 mm. and the other 234.3 mm. in length. The muscular tunic of the former consisted of a circular layer and a longitudinal layer. The latter showed the presence of oblique fibers as well as the longitudinal and circular layers.

One of the few papers describing the stomach of the newborn was published by Fleischmann, in 1875, as follows:

"The ring musculature of the esophagus surrounds the cardia in eccentric circles which become gradually weaker; they circle to the right, bringing the center to the left periphery of the cardia.

"The principal direction of the descending longitudinal fibers of the esophagus, which are superficial to the circular fibers, is towards the small curvature, in the middle of which they diverge toward the aforementioned longitudinal fibers, running laterally, and here disappear underneath them.

"The intrinsic musculature of the stomach consists of compact but freely anastomosing fibers arranged about the main axis in ring formation. These show at the two extremities of the stomach an irregular relationship towards each other.

"The child's stomach does not have oblique fibers; I also note, after some growth, the absence of longitudinal fibers which Henle has found in adults. These are said to originate from the pyloric valve."

THE EARLY HISTORY OF THE GASTRIC MUSCULATURE

The development of the circular layer. The development of the stomach from its first appearance as an expansion of the primitive gut, already described at 6 mm., up to the establishment of the circular layer at 24 mm., is characterized by a rapid growth of the organ with a continuous diminution in the relative thickness of the mesenchmya of its walls. At 6 mm. the thick lining epithelium of columnar cells shows four rows of nuclei, and the surrounding mesenchymal cells, while somewhat scattered and unorganized, are slightly condensed and mark the first appearance of the stratification of the gastric wall. The histologic picture at 7 and 7.5 mm. is essentially the same as in the 6 mm. embryo. At 11 mm. differentiation has already begun and the myoblasts can be seen arranged circularly, while the mucosa has become relatively thinner. The dorsoventral and lateral diameters of the stomach rapidly become greater and at 12 mm. the myoblastic layer is markedly thickened in the region of the future circular layer. From 12 to 17 mm. there is a remarkable growth of the stomach. In the former stage the gastric wall still consists of three primitive layers, entodermal epithelium, mesenchyma including a myoblastic layer, and peritoneal epithelium. The latter stage, however, shows a further condensation of the mesenchyma indicating an actual transformation to circular fibers which is best defined along the right side of the cardia and on the lesser curvature, but which can be identified over the greater portion of the organ. Between this condensed zone and the lining epithelium is a uniform layer of the mesenchyma invaded by numerous blood vessels and nerves.

The circular layer is complete at 24 mm. and is definitely thickened over the pylorus. The fundus has already developed and is completely invested with a layer of the circular fibers. The fibers of the fundus are arranged around a short seam at its apex, around which they describe circles with gradually increasing diameters (Fig. 1, c). Inferiorly, along the greater curvature, they blend imperceptibly with those of the circular layer which surrounds the rest of the organ. Superiorly, over the cardiac incisura, as the diameters of the fiber circles increase they cannot be distinguished from the oblique fibers which lie in this angle;

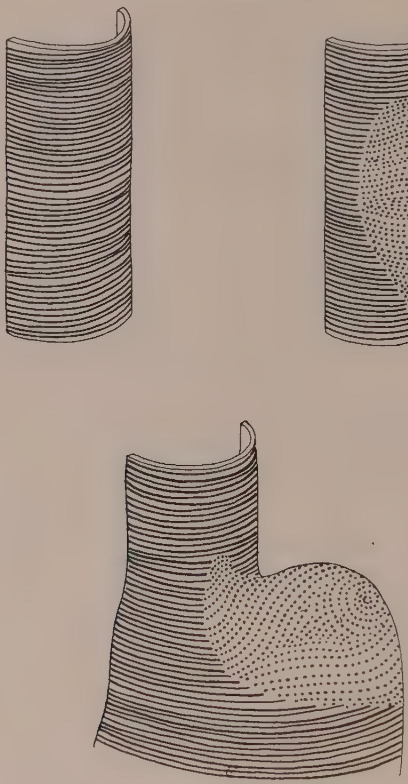

Fig. 16.—Scheme illustrating the formation of the oblique fibers and the circular layer of the fundus.

while on the anterior and posterior walls as these circular fibers approach the corpus they become intermediate between the oblique fibers and the "true" circular layer. This arrangement was checked by graphic reconstruction (Fig. 17), and concurs with dissections of fetal stomachs. At this stage (24 mm.) another condensation of the mesenchyma marks the beginning of a lamina propria. Increased vascularization is everywhere apparent.

At 33 mm. the gastric wall shows a general increase in the circular fibers. The cells are more elongated and the sarcoplasm nearly obscures the nuclei. With continuous growth and differentiation the 41 mm. embryo shows a very high degree of organization in which the circular layer begins to exhibit continuity among its fibers. Together with an increased blood supply to the submucosa there appear scattered patches of a lamina muscularis mucosæ.

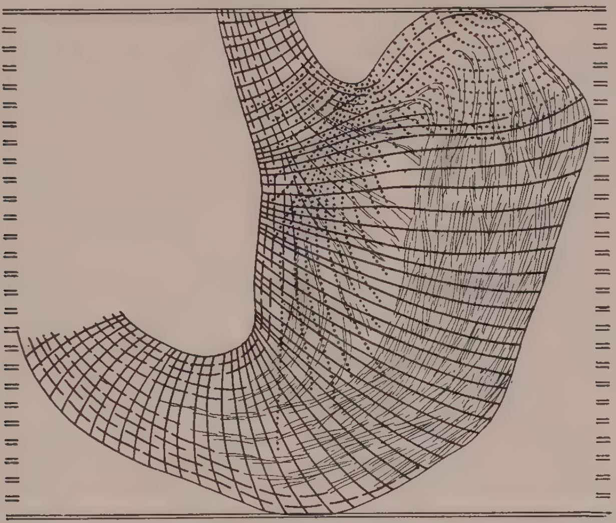

Fig. 17.—Diagrammatic representation of a graphic reconstruction. Stomach of an embryo of 65 mm. crown-rump length. (× 8.) (The double horizontal lines represent every fifth section.)

The last stage at which I studied the circular layer microscopically was in an embryo of 65 mm. Here I found a wide band of well formed circular fibers constituting a well defined, continuous coat pierced by numerous blood vessels which extend well around the greater curvature. The gastric wall measured 0.04 mm. in thickness, approximately one-fourth of which was occupied by the circular layer. The wall of the sphincter pylori measured 0.08 mm. and here the circular layer was 0.03 mm. in thickness. The lamina muscularis mucosæ was still incomplete, but could be identified in all sections.

THE LONGITUDINAL LAYER

The outer muscle coat appears first in more or less discrete, scattered bundles instead of as a simultaneous differentiation over the entire stomach, as is the case with the circular layer. Its subsequent development is much less precocious than that of the circular layer. At 17 mm. groups of cells can be seen just outside of the circular layer over the lower portion of the esophagus and certain parts of the stomach, especially along the margin of the lesser curvature and a short distance over the walls. Cells occupying the same position in the 24 mm. embryo show relatively small nuclei (in transection) surrounded by a dark area of differentiated cytoplasm. This is still more evident at 33 mm. and there is no doubt as to the presence of darkly staining myofibrillæ. The relations of these areas of differentiated mesenchyma to the vascular distribution are a constant feature. The entire gastric wall becomes progressively more vascular and blood vessels are very numerous in the region just outside the circular layer. Grouped about these vessels are areas of differentiated mesenchymal cells. Some of these are developing interstitial connective tissue cells, while the remainder constitute the foundation of the longitudinal section. In 100 sections taken at random in an older embryo (65 mm.), ninety-three demonstrated this feature without exception. The remaining seven showed the relationship to vessels, but at the same time showed certain scanty areas which apparently were independent of the vascular supply. In the 41 mm. embryo there is an increase both in number and distribution of the groups of muscle cells except over the mid-ventral and mid-dorsal portion of the walls of the corpus. In this situation they are very sparsely scattered and in some sections entirely absent. The increase is particularly apparent at the pylorus where there is an intermingling of the cells of the longitudinal layer and the circular layer. At 65 mm. a fenestrated layer of muscle, connective tissue, and blood vessels constitutes the longitudinal layer. Over the lesser curvature this layer is almost uninterrupted except for occasional penetrating vessels and nerves. Wide intervals occupied by connective-tissue cells only are found scattered over the rest of the organ. The continuity of the muscle-cell groups forming a syncytial layer is demonstrated by the graphic reconstruction shown in Figure 17. Within these groups are persistent aggregations of interstitial connective-tissue cells which appear to be very intimately related to the muscle elements of the layer.

THE OBLIQUE FIBERS

The oblique fibers appear as early as 24 mm. as a band of fibers coursing across the cardiac incisura and continuing in the direction of the digestive tube. With the very first appearance of a fundus there is obviously the beginning of a cardiac incisura. Even in these early stages when the circular layer is just differentiating from the mesenchyma of the digestive tube, a solid band of fibers can be seen covering the cardiac incisura. This band extends on the anterior and posterior walls, continues in the direction of the long axis of the stomach, and gradually disappears in the proximal part of the pylorus.

As the rings of the circular layer of the esophagus descend there is an interruption in their continuity in passing from the esophageal to the gastric wall. This interruption may be seen on the left side of the esophagus where the digestive tube expands to form the fundus. These fibers represent the beginning of the oblique fibers. The uppermost fibers are directly continuous with those of the esophagus. As this band approaches the fundus, its fibers are on the same plane with the circular layer and pass imperceptibly into it (Fig. 1, c). The oblique fibers merely represent a specialized part of the primitive circular layer and when the stomach is but a simple tube they cannot be identified as a separate entity. Once differentiated (24 mm.), however, the oblique fibers develop rapidly, and at 33 mm. may be seen in sections almost to the pylorus. At 41 mm. they are increased both in number and length. In the 65 mm. embryo they form a well developed band which is approximately 1.1 mm. in width in the middle of its course, while the lateral diameter of the stomach is only 4 mm. The oblique fibers terminate by joining the circular layer in the direction of the greater curvature (Fig. 15). With the exception of a few strands which course across the lesser curvature this band has the appearance of a unipenniform muscle (Fig. 5, c).

THE GASTRIC MUSCULATURE OF THE FETUS AND THE NEWBORN

The following observations on the later development of the gastric musculature were made chiefly on gross specimens. Of these, two were from embryos of 61 and 64 mm. (Figs. 1 and 2), and the remainder were from fetuses and newborn as previously listed. The results of this study, besides revealing the subsequent development of the muscle layers, afford an excellent check on the material studied in serial sections.

THE CIRCULAR LAYER (FIGS. 1 TO 14)

The arrangement of the circular fibers after their establishment at 24 and 33 mm. remains practically unchanged in all the later stages. The circular layer is well developed at birth and constitutes the greatest part of the gastric musculature. Its fibers are arranged in parallel rings approximately at right angles to the long axis of the organ. If traced downward from the esophagus there is a division of the circular layer into superficial and deep fibers about 5 mm. above the esophageal orifice. The latter will be discussed in connection with the oblique fibers. The former, crossing the subjacent oblique fibers at right angles, continue a short distance toward the fundus and are soon lost among the peripheral fibers of the "fundic whorl." The circular layer is disposed in concentric circles over the corpus and the pylorus, with closely set and freely anastomosing bundles of fibers. Numerous vessels and nerves pierce the gastric wall, especially along the curvatures, producing characteristic openings in the circular layer (boutonnières or Gefässlöcher). During the first year, probably as the result of increased activity of the stomach, there is marked thickening of the circular layer.

THE LONGITUDINAL LAYER (FIGS. 1 TO 14)

The development of the longitudinal muscular coat is not complete until the first year of postnatal life. During the fetal period and in the infant it is present as a coarsely fenestrated layer covering the entire stomach, excepting possibly a small area on the mid-dorsal and mid-ventral surfaces. This "bare area," however, becomes progressively smaller and in some instances among infants nearly two years old it may be entirely covered. For descriptive purposes the longitudinal layer is divided into three parts: first, those fibers which are continuous with the longitudinal layer on the left of the esophagus and pass over the fundus and the greater curvature to the pylorus; second, the fibers which occupy a similar position on the right side of the esophagus and course over the lesser curvature; and third, the intermediate group which cover the anterior and posterior walls to a varying degree.

The first group is directly continuous with the longitudinal layer of the esophagus and extends uninterruptedly in a uniform layer over the cardiac incisura on the dome of the fundus. Long strands of fibers can be stripped as far as the fundic apex where they are afforded an attachment. Likewise fibers of the greater curvature can be stripped to the apex, but very few, if any, actually cross it. This is explained by the presence of a narrow seam or raphé across the top of the fundus at right angles to the longitudinal fibers. (This raphé is often loosely referred to as the point of origin of the circular layer.) Here the ends of longitudinal fibers are bound down by a large amount of connective tissue. Fibers passing on either side of this area do not exhibit such an interruption, but continue to the pylorus in sweeping curves parallel to the greater curvature.

The second group of longitudinal muscle fibers is decidedly the best developed and can be stripped free from the underlying circular layer, without difficulty, from the esophagus to the pylorus. As the stomach narrows to form the pyloric antrum the first two groups are brought together forming a complete cylinder of longitudinal fibers covering this part of the organ.

The third group of longitudinal muscle fibers follows a course intermediate between the first two. As its fibers spread out in a fan-shaped manner they are often ill defined and many merge with the circular layer beneath (Fig. 12, d). In other specimens (Fig. 12, a), where these fibers are better developed, they pass behind the first group and blend with the subjacent circular fibers. When this is the case the entire gastric wall is invested with the longitudinal layer. After birth there is a notable increase in all three groups belonging to the longitudinal layer.

THE OBLIQUE FIBERS (FIGS. 1 TO 14)

After the longitudinal and circular layers of the corpus and pylorus are removed, there remain the oblique fibers and the circular fibers of the fundus. It will be remembered that at the time the circular layer is differentiated the anlagen of both the oblique and the circular fibers of the fundus are represented. At this time, 17 mm., there is only a slight suggestion of a fundus; however, the digestive tube is completely surrounded by an early circular layer. As the fundic diverticulum pushes to the left and upward the fibers which formerly covered it in parallel strands become festooned over this new formed dome (Fig. 16). Coincident with this development there appears a cardiac incisura and a bending of the lower circular fibers of the esophagus. This change in direction corresponds with the angle formed by the circular fibers of the right and left sides of the cardia, shown in all dissections. The latter band of fibers can soon be traced well along the gastric canal in the direction of the pylorus. If considered from the standpoint of simple mechanics the interrelationship and continuity of the layers of muscles of the stomach are much more easily understood.

The oblique fibers become separated from the circular layer at 24 mm. After surrounding the left side of the cardia, they pass beneath the circular layer. At first these fibers are very rudimentary, scarcely covering the narrow cardia. This stage is followed by a period of rapid development, and at 85 mm. (Fig. 3) the oblique fibers can be dissected free almost as far as the incisura angularis. From 85 mm. until birth there is a gradual increase in the number and extent of the oblique fibers, and their permanent relationship is established. In the newborn the oblique fibers extend as far as the pylorus and in some instances actually reach the proximal portion of the sphincter of the pylorus. The inferior fibers of this group (those lying adjacent to the circular layer of the fundus) are short and terminate early by passing into the circular layer and its surrounding connective tissue in the direction of the greater curvature. The remaining oblique fibers which course toward the pylorus are longer and have similar insertions at variable distances. On the side of the lesser curvature in the newborn certain of the oblique fibers invariably joined the circular layer (Fig. 11, c). Similarly, annular fibers belonging to the oblique layer encircle the lower end of the esophagus beneath the circular layer. The only change in this layer during the first year is the accumulation of a greater number of fibers, especially along the gastric canal. There is commonly an alteration in the form of the stomach after birth; it becomes elongated and slightly dilated. As a result the oblique fibers also become longer and the width of this band is increased.

SUMMARY AND DISCUSSION

The findings presented in this paper differ in certain fundamental respects from those in the literature. The first appearance of the transformation from the mesenchyma to muscle fibers may be made out at 17 mm., or at about seven weeks. At 33 mm., or about nine weeks, the longitudinal fibers are definitely established, and there is a relatively wide band of oblique fibers crossing the cardiac incisura. In the embryos of 41 and 65 mm. (nine and one-half and twelve weeks old respectively) there is an intimate intermingling of the longitudinal and circular fibers at the pylorus, suggesting the formation of the "tug muscle" (dilator pylori) as described by Cunningham. Thus, from nine to twelve weeks on, throughout subsequent development, the musculature of the stomach consists of three parts: the longitudinal and circular layers and the oblique fibers.

The limitation of the stomach musculature to two layers, as by Hyrtl (Gyllenskoeld), holds true for only a very short time. At about 17 mm., when the gastric musculature begins to form and before the appearance of the fundus, I could observe but two layers, the longitudinal and the circular. However, in subsequent stages, after the stomach had assumed its characteristic form (at nine weeks), the third layer of oblique fibers is universally present. At no time can four layers (Guéneau de Mussy) be demonstrated. Any such classification can only be for physiologic purposes. The simple arrangement of the longitudinal layer as given by Sappey has been shown to be inaccurate. Contrary to Larger, the fibers of this layer can be followed in a more or less continuous band over the fundus. While a few can be seen terminating at the apex, others appear to take origin at this point and continue over the greater curvature. The description of the musculature of the adult stomach as given by Birmingham and Forssell, more nearly coincides with the condition found in the fetus and newborn.

The arrangement of the gastric musculature of older human fetuses and the newborn may be summarized as follows: The stomach is everywhere covered (as by the oblique fibers on the mid-dorsal and mid-ventral surfaces) by two layers of muscle, in some places by three. This is true of the dorsal and ventral surfaces of the walls of the cardia and along either side of the lesser curvature. The circular layer is well developed and forms an almost complete layer around the gastric tube. The term "almost complete" is used advisedly because the circular fibers covering the cardiac incisura and on the lower extremity of the esophagus are considered as a separate layer, the oblique fibers. The longitudinal layer usually covers the entire stomach, but is very thin, particularly along the greater curvature and on the dorsal and ventral surfaces. In the latter positions it may even be absent. Beneath the longitudinal and circular layers are the oblique fibers. On the left side of the esophageal-cardiac juncture, the region of the cardiac incisura, the oblique or innermost layer bears the same relation to the digestive tube as the circular fibers on the right side. This band is continuous above with the deep circular fibers of the esophagus and below with the circular fibers of the fundus. Its fibers course over the lateral wall in the direction of the pylorus and finally become a part of the overlying circular layer. The layer of oblique fibers is not of uniform width or thickness, but adapts itself to changes in position and function.

At birth there is a marked dilatation of the stomach due to constant swallowing of a large amount of air, and after the infant begins to nurse there is a further increase in gastric capacity together with a slight change in the form of the organ. A general thinning of the musculature, particularly of the walls and the fundus, results. The relationship of the layers of muscle, however, remains unchanged at three months. During the latter half of the first year (ten months) there is slight compensation through the rapid postnatal growth of the organ, but the gastric wall is still extremely thin and more easily dilated (artificially) than the fetal stomach.

The methods of growth and development differ somewhat in the various layers of the musculature of the stomach. The circular layer is differentiated from the mesenchyma in situ as a sheet surrounding the entire gastric epithelial tube. The longitudinal layer develops as maculations of myoblasts over the stomach and these later anastomose. This confluence gives rise to the fenestrated arrangement characteristic of the stomach in the fetus and newborn. Usually these collections of myoblasts arise in close relation to the larger vascular sprigs in this region. The oblique fibers, as such, begin in a limited area on the left side of the cardia and extend along the gastric canal after the formation of the fundic diverticulum.

CONCLUSIONS

1. The fundament of a muscular coat of the stomach is first observed at 17 mm. (about seven weeks).

2. At the time muscle fibers first appear in the gastric wall, there are but two fundamental layers: the longitudinal and circular.

3. The circular layer of the fundus appears to form concentric whorls about a central raphé as the result of the rapid growth of that part. The actual appearance of annular fibers was not observed until during the first part of the fetal period.

4. Coincident with the development of the fundus (24 and 33 mm.,

eight and nine weeks), the number of layers is increased to three by the development of oblique fibers from the circular layer.

5. The development of the longitudinal fibers is intimately related to the vascular supply to the gastric wall.

6. In the later fetal months the musculature of the stomach consists of: (a) a circular layer completely investing the organ; (b) a coarsely fenestrated longitudinal layer, very thin or absent over the mid-dorsal and mid-ventral portions of the wall; and (c) oblique fibers marking a primitive gastric canal as far as the incisura angularis.

7. The stomach of the newborn is characterized by a very thick circular layer. The longitudinal layer is less scattered than in the fetus, and usually covers the entire organ. The oblique fibers can be traced to the proximal portion of the sphincter of the pylorus.

8. Changes in the stomach musculature during the first year include an interstitial increase in all three muscle layers. The slight alteration in the form of the stomach has no effect upon the relationship of the three layers.

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A STUDY OF THE PATHOLOGIC CONDITIONS ENCOUNTERED DURING AND FOLLOWING THE RELIEF OF EXPERIMENTAL OBSTRUCTIVE JAUNDICE COMPARED WITH SIMILAR PATHOLOGIC CONDITIONS IN MAN*

LEO P. BELL.

My experiments were conducted for the purpose of studying the effect on the liver of obstruction of the common bile duct and the regenerative processes which occurred after the flow of bile was reëstablished.

In summarizing data from the literature from studies of cirrhosis in man, and of portal and biliary cirrhosis produced experimentally in rabbits and dogs, the following points are emphasized:

1. Many chemical irritants and mechanical means, including twenty-four different technics, have been used to produce experimental cirrhosis.
2. The response of the liver depends on the nature of the irritant or poison and the manner of application.
3. To produce cirrhosis parenchymal cells must be destroyed by mechanical means, such as ligation of the common duct, or by the introduction of toxic substances through the portal vein.
4. Experimental cirrhosis in animals is comparable to that found in man, with regard to parenchymal cell destruction, biliary duct proliferation, connective tissue proliferation, and parenchymal cell regeneration. The microscopic and macroscopic pictures are otherwise dissimilar.
5. Cirrhosis in man is due to a combination of factors which have not been identified experimentally.
6. Cirrhosis in man is due to attempts to repair damage done by successive waves of toxins producing parenchymal cell destruction through the blood stream and biliary apparatus. It is assumed that this chronic process or cell injury covers a considerable period of time.

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* Abridgment of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, 1921. From the Section on Experimental Surgery, Mayo Clinic.

7. Atrophic cirrhosis in man may not be due to connective tissue contraction. Compression of liver tissue in hypertrophic cirrhosis is due to new growth of parenchymal tissue.

EXPERIMENTAL PROCEDURE

All the experiments were performed on dogs under ether anesthesia and sterile technic. At the first operation a small specimen of liver tissue was removed for histologic study, and then the common bile duct was doubly ligated and sectioned. At various periods after obstruction, varying from four to seven weeks, another specimen of liver tissue was secured and the flow of bile reëstablished. Various methods were attempted for relieving the obstruction. A cholecystoduodenostomy was found to be the most satisfactory. Specimens of liver tissue were obtained at various times following the cholecystoduodenostomy.

RESULTS

Specimens of the liver of five dogs were obtained as described and studied in detail. Briefly the changes noted were:

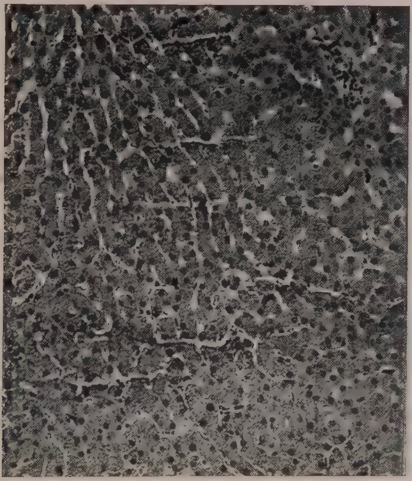

Fig. 18 (Dog E88).—Specimen of normal liver, November 12, 1920. Hematoxylin and eosin. (× 100.)

1. The first specimens of liver tissue obtained (before operation) were normal.
2. The second specimens of liver tissue obtained (four to seven

weeks after obstruction of the common bile duct) showed: (a) an increase in proliferation in connective tissue, (b) new formation of capillaries, (c) proliferation of interlobular biliary ducts, (d) the parenchymal tissue as a whole not markedly affected, and (e) biliary pigment in the peribiliary spaces.

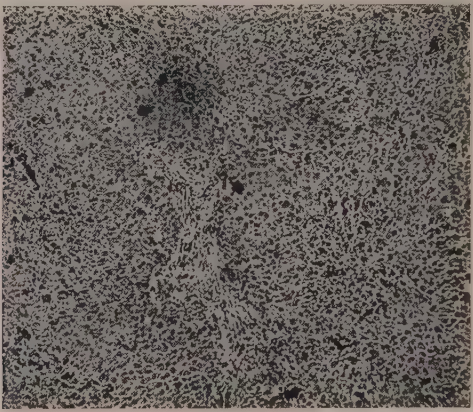

Fig. 19 (Dog E88).—Liver twenty-eight days after obstruction, December 10, 1920, showing marked destruction of parenchymal tissue, liver regeneration around the peribiliary spaces, and biliary pigment in the peribiliary spaces. Hematoxylin and eosin. (× 60.)

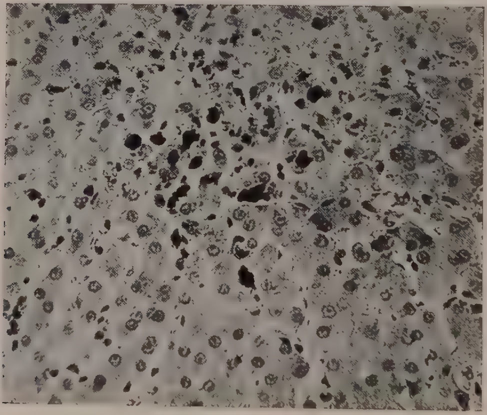

Fig. 20 (Dog E88).—Higher magnification of the specimen shown in Fig. 19. All parenchymal tissue is of new formation, showing the grouping of newly formed liver cells into trabeculæ as they push away from the peribiliary spaces. Hematoxylin and eosin. (× 200.)

3. The succeeding specimens of liver tissue obtained (thirty-three

to forty-one days after the flow of bile was reëstablished) showed: (a) little evidence of the previous obstruction in the liver parenchyma, (b) a moderate amount of connective tissue in the peribiliary spaces; most of the sections did not show marked evidence of formation of new connective tissue; (c) new formation of liver parenchyma still in evidence, and (d) little evidence of new formation of connective tissue.

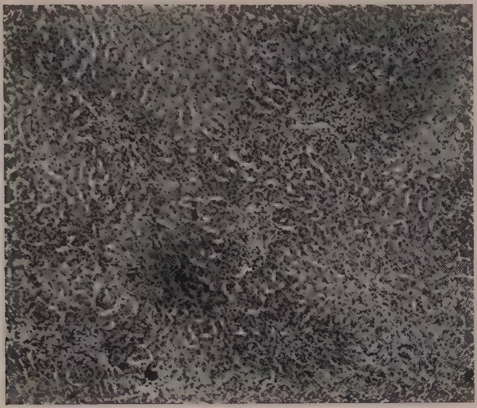

Fig. 21 (Dog E88).—Specimen of liver forty-two days after cholecystoduodenostomy, January 21, 1921, showing newly formed parenchymal tissue around the peribiliary spaces, arrangement of newly formed parenchymal tissue into trabeculæ of normal appearance, and numerous proliferating bile capillaries. (× 60.)

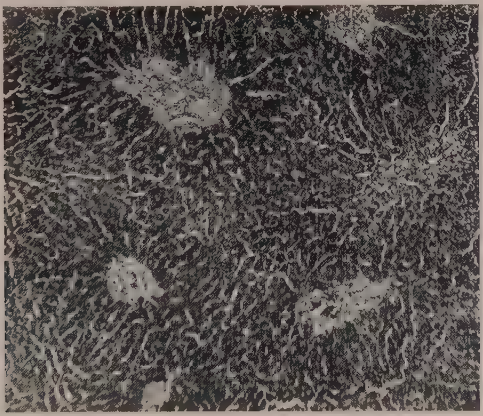

Fig. 22 (Dog E88).—Specimen of liver eighty-one days after relief of obstruction, March 2, 1921, showing parenchymal tissue normal in appearance and arrangement of trabeculæ, evidence of peribiliary connective tissue of old appearance, and definite arrangement of capsule of Glisson with excess of fibrous tissue. (× 60.)

DISCUSSION

Previous writers differ somewhat in their findings and interpretations of results obtained from experimental obstructive jaundice. Joannovics emphasizes that biliary obstruction must be sufficient to produce destruction of parenchyma if connective tissue is to be formed in considerable amounts. He considers that other factors, not met experimentally, are present in biliary cirrhosis in man. Parenchymal destruction and connective tissue and biliary hyperplasia is the essential picture.

Fischler obtained consistent pathologic changes following obstruction.

Porri shows that parenchymal destruction is much greater in obstruction associated with jaundice. He described the marked fatty degeneration of parenchymal tissue.

Fiessinger and Rowdowska describe stone-like pigment infarcts in microscopic sections. They consider later stages of biliary cirrhosis in a rabbit to be an annular or encystment form of cirrhosis. They consider the very early lesions of parenchyma to be owing to toxicity of bile.

Richardson has made a most careful study of the findings in livers of rabbits with obstruction. His results agree with those reported herein.

From my own experiments and the data of other investigators, it would seem that the parenchymal tissue goes through a process of destruction graded from mild to severe cell injury with fatty degenerative changes, before complete destruction takes place. Richardson, Porri, and others have emphasized this fatty change in liver parenchyma. It would seem that the cause of parenchymal tissue destruction is poisoning by bile pigment,[2] increased secretory pressure in the interlobular biliary ducts, and loss of secretory function of the liver parenchyma, as shown by ultimate destruction as the chronicity of obstruction develops.

Destruction of parenchymal tissue depends on the duration of obstruction. After parenchymal destruction, connective tissue rapidly proliferates and replaces the spaces formerly occupied by parenchymal tissue. This proliferation is demonstrated by the presence of mitotic figures and the embryonic appearance of the cells and, apparently, is not affected by continued obstruction, for mitotic figures are seen forty-nine days after obstruction. Bile pigment is not toxic to connective tissue cells and, apparently, acts as a stimulant to new growth by irritative action. It seems to be toxic to endothelial cells of blood vessel as manifested by petechial and massive hemorrhage in the parenchymal tissue. New growth of blood capillaries can be explained in part by the increase of necessary blood supply to the newly formed connective tissue and biliary ducts. The blood seen in the sections of liver tissue may be owing to congestion of the liver and rupture of the endothelial lining of the blood vessels because of injury to the endothelial cells. The interlobular biliary capillaries of the liver apparently are stimulated to growth by bile pigment and increased intrabiliary pressure. Besides, there is an unexplained physiologic factor which causes the change of interlobular ducts into liver trabeculæ as the metabolic needs of the gland increase or destruction of parenchymal tissue progresses.

After relief of obstruction complete regeneration takes place, the rapidity of which depends on the duration of obstruction. The newly formed liver parenchymal tissue, arising from the undifferentiated interlobular bile capillaries, is pushed outward from the vicinity of the peribiliary spaces and forms in trabeculæ with the undestroyed liver parenchyma. The connective tissue undergoes the shrinkage of age, becoming shorter, narrower, and flattened. After two months there is little evidence of excess of connective tissue in the interlobular spaces; it is still present in the peribiliary spaces, but only in moderate amounts.

The bile capillaries in the peribiliary spaces are converted into liver trabeculæ. As this process goes on bile capillaries are often seen far removed from the peribiliary spaces. They are completely surrounded by newly formed parenchymal tissue in many cases. It is readily seen that these bile capillaries, before they are surrounded by the growth of parenchymal tissue, form the peribiliary spaces. After two months only moderate excess of biliary capillaries is seen in the peribiliary spaces. The blood vessels are also slightly in excess. From this I conclude that the period of regeneration following obstruction covers from two to four months following the release of obstruction. The factors controlling complete regeneration are the amount of destruction to liver parenchyma and the duration of obstruction.

Repair in the liver, according to Marchand, takes place in three ways: (1) hyperplastic proliferation of the larger intact remains of the gland parenchyma, (2) proliferation of isolated clumps of liver cells, or remains in the region of the most intense destruction, (3) proliferation of the interacinar bile ducts which aid in forming new liver strands.

Stroebe says that repair takes place by ingrowth of biliary sprouts from interlobular bile ducts toward the central veins of the partially destroyed lobules. He believes that there is a gradual transformation of the epithelial cells of the bile duct into parenchymal tissue. He denies the views of Marchand on his first and second hypotheses. Barbacci is of the same opinion concerning the views of Marchand. He believes that partly destroyed parenchymal cells will not regenerate.

Podwyssozki and Ponfick have shown experimentally that regeneration of liver following destruction or removal of a large part of the parenchymal tissue is brought about by mitosis of the parenchymal cells from interlobular ducts of the biliary apparatus. True hyperplasia was observed on extirpation of large portions of the liver parenchyma by Ponfick and von Meister.

MacCallum, investigating acute yellowa trophy of the liver in man, finds that regeneration of the parenchymal tissue takes place in two ways: (1) if scattered isolated lobules remain after extensive destruction, hyperplasia of this tissue takes place rapidly, and the interlobular bile capillaries are not concerned in the regeneration of the parenchymal tissue, this supports the views of Ponfick on experimental functional hypertrophy, (2) if all, or nearly all of the parenchymal tissue is destroyed, the bile capillaries rapidly multiply and their epithelium becomes differentiated into parenchymal tissue. The former supports the views of Ponfick and the latter is more in keeping with the experimental work of Podwyssozki, who finds that granulation tissue forms following removal of portions of liver tissue and that the bile ducts grow into the granulations and form parenchymal tissue by rapid differentiation. Pearce and Richardson have similar conceptions.

In studying the repair of liver tissue in serial sections taken during and following release of obstruction produced by ligation of the common bile ducts in dogs, I found that a large amount of repair of parenchymal tissue has taken place in dogs after ligation for twenty-eight days. There was not the extensive destruction found by Richardson in early stages of obstruction in rabbits, and there was practically no evidence of mitosis of parenchymal tissue. The bile pigment had poisoned the parenchymal tissue to such an extent that regeneration by mitosis was impossible. Richardson did not find mitotic figures in the parenchymal tissue of rabbits after twenty-four hours of obstruction. Regeneration of parenchymal tissue, as seen from periods of twenty-eight to forty-nine days of obstruction, was entirely from the undifferentiated cells of the interlobular biliary capillaries. The destruction of parenchymal tissue takes place from the peribiliary spaces toward the center of the lobule. Bile capillaries rapidly proliferate and form many buds which push into this destroyed or injured tissue. The differentiated cells form into masses which, in turn, may form trabeculæ immediately and push toward the center of the lobule. The trabeculæ may be formed also by the growth of the biliary ducts outward with loss of their lumen and differentiation into typical parenchymal tissue which, as regeneration continues, unites with other trabeculæ to form liver tissue of normal appearance.

It would seem that newly formed parenchymal tissue resists injury from bile for some time after regeneration. I am in doubt as to the secretory activity of the newly formed parenchymal cells. Inability of newly formed parenchymal tissue to secrete bile until obstruction is relieved might account for the gradual loss of the power of the liver to secrete bile as obstruction progresses. It is shown that the newly formed parenchymal cells do secrete bile following relief of obstruction, but I believe that they do not function as extensively as does normal parenchyma when there is no obstruction. It is logical to believe, therefore, that even though parenchymal cells appear normal in function, as seen microscopically during bile stasis, their secretory powers are quite limited. The picture seen in some sections after long periods of obstruction is as if the new liver tissue surrounding the peribiliary spaces were being pushed gradually toward the portal or interlobular spaces. It appears that the greater part of the lobule had been replaced by newly formed parenchymal tissue, during obstruction of from forty-two to forty-nine days. The work of other experimenters has shown that regeneration is very rapid if there is only one wave of intoxication. The source of repair, as shown by MacCallum, depends on the amount of destruction of parenchymal tissue. It is probable, therefore, that no highly specialized secretory cell can undergo mitosis when subjected to repeated or continuous injury. During poisoning of the parenchyma in obstructive jaundice, therefore, regeneration can come only from the bile capillaries. Rate of regeneration is definitely slowed up as the chronicity of the poisoning is established.

SUMMARY

A histologic study was made of liver tissue before and after various periods of occlusion of the common bile duct and after relief of such obstruction at the end of various periods after occlusion. A brief review of the changes taking place in the liver after obstruction of the common

bile duct is given, as well as a description of the recovery which follows when the flow of bile is reëstablished. Return of the liver to normal following relief from obstruction is rapid. From two to three months after such relief, there is little evidence of the previous obstruction.

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THE EFFECT OF MAGNESIUM SULFATE ON THE SECRETION OF BILE: EXPERIMENTAL STUDY*

EMMETT B. FRAZER

During the last few years much has been written on drainage of the biliary tract by means of lavage of the duodenum with magnesium sulfate solution. It is my purpose to report here the results of experiments undertaken to determine the effect, if any, of magnesium sulfate on the secretion of bile.

METHOD OF EXPERIMENTATION

Dogs were used in all experiments, and ether anesthesia and rigid sterile technic were employed. Permanent biliary fistulas were made according to the method worked out in this laboratory.[2] In certain experiments the gallbladder was removed; in others it was not.

The fistulas were made in two-stage operations. If the gallbladder was to be removed, it was done during the first stage, which consists of transplanting the duodenum just beneath the skin and fascia. About two weeks later, when the wound had healed, the second stage operation was performed. At this time the skin only was cut through; the common duct was easily located at the point where it entered the duodenum. The duct was cut in two at its distal extremity, a small rubber catheter was introduced into its lumen, and the end of the duct fastened in the suture line. Two or three days later the rubber tube was removed and a well draining biliary fistula resulted. Ascending infection rarely occurred and the dogs usually did well and sometimes lived for many months.

After the fistulas were draining properly the animals were fastened on a frame and made as comfortable as possible. The room was kept quiet during observation, thus reducing to a minimum any psychic stimulation. After a little training the animals lay quietly for many hours at a time. A small catheter or metal cannula was introduced into the fistula and bile was collected continuously in fifteen minute fractions.

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* From the Division of Experimental Surgery and Pathology. Reprinted from Journal of the American Medical Association, 1922, lxxix, 1594–1596.

RESULTS

The normal rate of flow of bile was first determined. Observations were made on animals recently fed and on those from which food had been withheld for twelve hours. No great difference in the rate of flow of bile was noted; however, the rate was somewhat more uniform under fasting.

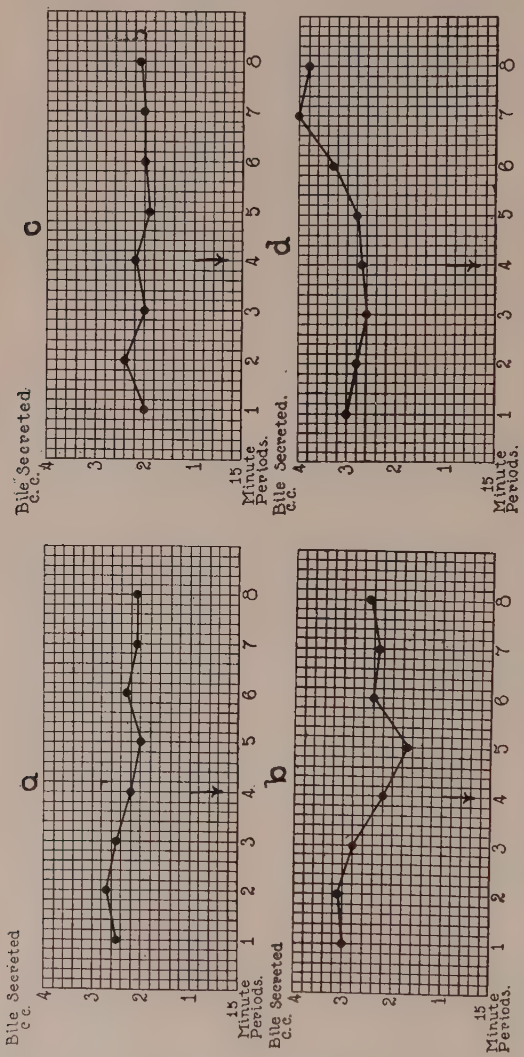

FIG. 23.—a, Normal flow of bile; control experiment; b, flow of bile before and after magnesium sulfate intraduodenally, arrow indicates injection; c, flow of bile before and after magnesium sulfate intravenously, arrow indicates injection; d, flow of bile before and after bile had been injected into the duodenum, arrow indicates injection.

In one series of experiments magnesium sulfate was injected into the lumen of the duodenum by means of a hypodermic syringe. This was very easy and caused the animal little or no inconvenience, as the duodenum had been transplanted just beneath the skin and was well fixed in its new position. The method offers an excellent means of studying the pharmacologic action of other drugs introduced under physiologic conditions without first being passed through the stomach.

In another series of animals the magnesium sulfate was introduced intravenously. The salt was dissolved in distilled water, boiled, and left to cool to body temperature. Injections were made into superficial veins of the leg.

Only those experiments in which the animals were quiet and the experimental conditions ideal were considered. The effect of the intraduodenal and intravenous injections on the flow of the bile was carefully noted. Each experiment was controlled by determination of the normal flow of bile in cholecystectomized and noncholecystectomized animals, and by determination of the normal flow of bile for each animal (Table 1 and Fig. 23, a).

TABLE 1

Normal Rate of Flow of Bile in Dogs

Cubic centimeters bile every fifteen minutes.	Gallbladder.	
	Removed.	Not removed.
First	1.4	3.4
Second	1.6	1.8
Third	0.8	1.0
Fourth	1.1	3.0
Fifth	1.1	2.5
Sixth	1.2	2.6
Seventh	1.2	2.0
Eighth	1.1	1.8

Bile was collected in fifteen minute fractions for one hour in order to determine the normal flow. The solution of magnesium sulfate was then injected into the duodenum and observations on the flow of the bile were made for one hour in fifteen minute fractions (Table 2 and Fig. 23, b). Similar observations were made before and after intravenous injection of magnesium sulfate (Table 3 and Fig. 23, c).

TABLE 2

Effect On the Flow of Bile of Magnesium Sulfate Injected Into the Duodenum in Dogs

Cubic centimeters bile every fifteen minutes.	Gallbladder.	
	Removed.	Not removed.
First	4.8	2.6
Second	4.2	1.2
Third	3.5	1.4
Fourth	2.7	1.7
Cubic centimeters bile secreted following injection at fifteen minute intervals.	5 gm. magnesium sulfate in 20 c.c. water injected into duodenum.	10 gm. magnesium sulfate in 30 c.c. water injected into duodenum.
First	2.0	0.8
Second	2.5	1.4
Third	2.6	0.1
Fourth	2.8	0.8

TABLE 3

Effect On the Flow of Bile of Magnesium Sulfate Injected Intravenously in Dogs

Cubic centimeters bile every fifteen minutes.	Gallbladder.	
	Removed.	Not removed.
First	1.9	2.0
Second	2.0	2.2
Third	2.0	1.2
Fourth	2.1	1.6
Cubic centimeters bile secreted following injection at fifteen minute intervals.	1.2 gm. magnesium sulfate in 10 c.c. water intravenously.	2 gm. magnesium sulfate in 15 c.c. water intravenously.
First	1.9	1.2
Second	2.0	1.2
Third	2.0	1.2
Fourth	2.1	1.4

In order to test the validity of the procedure of the intraduodenal injection of magnesium sulfate, experiments were carried out in which fresh bile was injected into the duodenum in the same manner (Table 4 and Fig. 23, d). The experiment was controlled by another in which normal saline was used instead of bile.

TABLE 4

EFFECT OF INTRADUODENAL INJECTION OF BILE IN DOGS

Cubic centimeters bile every fifteen minutes.	Gallbladder not removed.	
First	2.1	3.0
Second	2.0	2.8
Third	1.6	2.5
Fourth	1.7	2.7
Cubic centimeters bile secreted following injection at fifteen minute intervals.	15 c.c. normal saline injected intraduodenally.	15 c.c. fresh bile injected intraduodenally.
First	1.2	3.0
Second	1.0	3.5
Third	1.5	4.0
Fourth	1.7	3.8

COMMENT

The experiments outlined were undertaken in order to determine whether magnesium sulfate introduced directly into the duodenum or into the circulation would cause any change in the volume or in the character of the bile. The data tabulated are representative of observations on many dogs.

The technic employed was simple and easily executed. When the common duct was cut at its entrance into the duodenum any nerve path which might have passed by this route was also severed. If a nerve reflex was dependent on such a route it would have been abolished.

It was found that the rate of flow of bile in the control experiments was more uniform when the animals were fasting; therefore, any fluctuation in the rate of flow after the injection of magnesium sulfate could best be determined in the fasting state.

After intraduodenal injection of magnesium sulfate the duodenum, which was clearly visible through the skin, at first contracted and then remained markedly relaxed for from thirty minutes to one hour. This initial contraction was probably owing to mechanical stimulation by introduction of the needle and the solution.

CONCLUSIONS

The results of our experiments were entirely negative. When magnesium sulfate solution was injected directly into the duodenum of dogs or injected into the circulation there was neither acceleration of the rate of flow of bile nor change in the color. In many instances the rate was even somewhat retarded.

When bile was injected into the duodenum there was a denifite, prompt increase in the flow of bile.

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RENAL AND HEPATIC INSUFFICIENCY IN OBSTRUCTIVE JAUNDICE*

DUNCAN PARHAM

Operations on patients with obstructive jaundice offer three avenues of danger aside from the so-called accidents of surgery: (1) hemorrhage, (2) uremia, and (3) hepatic insufficiency.

Hemorrhage.—The extreme danger from hemorrhage in the presence of jaundice is well known. In a previous review of the necropsy findings in twenty-nine cases of obstructive jaundice it was shown that serious postoperative hemorrhage occurred in more than 50 per cent. A method of preoperative preparation of patients was described. That such preoperative preparation has met with success is evident from the fact that in the last series of thirty-four patients with obstructive jaundice who received this preparation, there was but one case of serious postoperative bleeding.

Uremia.—A large percentage of patients with obstructive jaundice have a certain amount of albumin and some casts in the urine. If albumin is slight and casts are few, the blood urea only moderately elevated, and the urine output satisfactory, operation is warranted, provided a normal blood coagulation time exists.

Case 1 is illustrative of the fact that renal insufficiency occurs as a terminal event in cases of obstructive jaundice in which operation has not been performed.

Case 1 (A313919). Mr. J. V., aged sixty-eight years, entered the Clinic October 5, 1921, with a history typical of gallstone colic followed by jaundice which became deeper progressively and was marked at the time of examination. The stools were clay colored. A twelve-hour specimen of urine contained a large amount of albumin, hyaline and granular casts, and leukocytes. The coagulation time of the blood was nineteen minutes.

The patient was referred to the hospital October 8 for preoperative preparation, but because of the nausea and vomiting it was thought best first to place him under observation for twenty-four hours. During the next forty-two hours the jaundice deepened;

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the patient passed only 180 c.c. of urine, in spite of a subcutaneous intake of 1800 c.c. of normal salt solution. Occasionally blood was noted in the vomitus. The patient became restless and noisy, then drowsy and stuporous. October 10, the day before his death, the blood urea was 294 mg. for each 100 c.c. and creatinin 5.8 mg. Necropsy revealed chronic diffuse nephritis and hemorrhage into the gastro-intestinal tract. An impacted stone in the common duct was the cause of the complete obstructive jaundice. Operation was deferred on account of the high coagulation time of the blood and the renal insufficiency.

In a large percentage of the cases of obstructive jaundice after ether anesthesia was used the blood urea became double the preoperative quantity the second or third day after operation. When local anesthesia, by infiltration of the abdominal wall, was combined with a slight amount of ether (usually 30 to 75 c.c.), the rise in the blood urea was noted in a smaller proportion of the cases. As a rule this rise forty-eight to seventy-two hours after operation gradually disappears, and without other trouble the patient has a steady normal convalescence. Unfortunately some patients do not get on so well. If, after operation, there is an increase in the cholangitis, or if biliary drainage becomes insufficient, there may be a greater retention of bile with an increase in the jaundice and in the blood coagulation time and a concomitant increase in nephritis with rising blood urea. These patients sometimes show an alarming picture of uremia and may not recover.

The findings in a typical case of obstructive jaundice in which the patient died of renal insufficiency secondary to operation are as follows:

Case 2 (A373925). Mr. L. F., aged sixty-four years, was examined in the Clinic October 3, 1921. Six weeks before he had developed jaundice and generalized pruritus, clay stools, and marked constipation. The urine contained albumin 2 (on the scale of 1 to 4) and casts 1. The coagulation time of the blood was ten minutes. Cholecystogastrostomy for carcinoma of the head of the pancreas was performed. The third day after operation urinary retention necessitated catheterization; marked hematuria followed. The fourth day after operation the blood urea was 228 mg.; it rose to 360 mg. and the creatinin to 3 mg. on the eighth day. The patient was transfused twice; he died on the ninth day apparently from uremia. Necropsy revealed marked nephritis, blood in the urinary bladder, in the gallbladder, and in the gastro-intestinal tract. Neither this patient nor the patient in Case 1 was given calcium chlorid intravenously.

The only treatment indicated in these cases is for any impending uremia. Drains should be carefully inspected to see that they are not obstructed.

Hepatic insufficiency.—Too little consideration has been given to the incompetent liver as an obstacle to the recovery of the patient with obstructive jaundice. Because of the remarkable compensatory and regenerative abilities of the liver it has been difficult to obtain exact data with regard to liver failure. It may be safer to regard these patients as suffering from lack of sufficient hepatic function rather than from hepatic insufficiency. The trouble may not be so much an intrinsic lack of vigor of the liver cell as the liver's inability to function properly because of obstruction in the avenue of excretion. The term "cholemia" is sometimes used to signify the symptoms accompanying the retention in the blood of toxic products which the liver has failed to eliminate. Cholemia means bile in the blood, but as a clinical expression it is often used loosely to mean almost any untoward syndrome occurring in jaundiced patients. Terms such as cholemic nephritis and cholemic hepatitis might be used. It would seem better simply to use the word as meaning the presence of bile in the blood. Be this as it may, it is certain that patients with common duct obstructions present a so-called biliary cirrhosis of various degrees, more correctly central atrophy and cholangitis. When this is so marked that the liver is a yellow, bile stained organ, shrunken to two-thirds its normal size, the prognosis as to the outcome is very serious. An alarming percentage of patients thus affected die from lack of hepatic function.

At necropsy in such cases the liver is small and yellow, sometimes weighing less than 1000 gm., although in some instances it may be larger than normal. There are many bile thrombi in the canaliculi of the central portion of the lobules. The hepatic cells of the central zone are atrophied, although there is a great deal of fairly good liver tissue in the periphery of the lobules. However, the latter often shows slight hydropic change or a moderate amount of fine fat granules as revealed by sudan III stain. There is scarcely enough definite abnormality present to make the liver inadequacy recognizable from a morphologic standpoint. On the other hand, the better known syndrome of renal insufficiency cannot always be diagnosed at necropsy.

Clinical picture of hepatic insufficiency.—Usually the first two to eight days after operation the course is uneventful. Biliary drainage and urinary output are normal. Fluids are taken well. The pulse and temperature are normal. One of the first signs of the onset of trouble is paling and thinning of the bile with marked increase in the flow. This profuse cholerrhagia does not continue long, but the bile remains thin. The patient begins to grow weaker, the pulse loses volume, and the temperature becomes subnormal. Restlessness and irritability develop, with great fatigue and muscular weakness. Soon regurgitant vomiting follows intake of liquids by mouth, and little taken by rectum is retained.

Jaundice does not deepen markedly, but there is an increasing pallor beneath the icteric hue, the face becomes drawn, and the eyes anxious. The patient grows progressively weaker and finally dies. The urinary output remains proportional to the fluid intake throughout, and the urine reveals little or no evidence of marked nephritis. The blood urea remains persistently low.

The histories of four cases are presented herewith in which there was a definite clinical picture of the lack of hepatic function.

Case 3 (A383124). Mrs. G. B. B., aged sixty-one years, presented herself at the Mayo Clinic for examination February 2, 1922. She had complained of attacks of epigastric pain for forty-five years, more severe for the last ten years. Four years before, the jaundice first appeared during such an attack. July, 1918, cholecystostomy was performed elsewhere; one large stone was removed. Attacks of nausea, vomiting, and jaundice persisted, and in December, 1920, cholecystectomy was performed elsewhere. Following this, fluctuating jaundice persisted, and clay stools, constipation, and general pruritis appeared.

Examination revealed jaundice. The systolic blood pressure was 144, the diastolic 84. The pulse was 72, and temperature 98.5. The patient weighed 101 pounds; her normal weight was 140 pounds. The hemoglobin was 68 per cent, the erythrocytes numbered 4,090,000, the leukocytes 8,900. The specific gravity of the urine was 1.021, albumin 0, sugar 0, casts 0, erythrocytes 0, and pus 1 (Scale of 1 to 4). Bile, urobilin, and urobilinogen were present.

February 5, the patient was sent to the hospital and preoperative preparation begun. The coagulation time was normal (four and one-half minutes, Lee and White method), nevertheless 10 c.c. of 10 per cent calcium chlorid was given intravenously. The blood urea was 20 mg. for each 100 c.c.

February 7, choledochostomy was performed for choledocholithiasis. The common duct was 2.5 cm. in diameter. Two stones were removed. Local anesthesia with whiffs of ether was used. Following operation the biliary drainage and urinary output were satisfactory, and the jaundice cleared slightly. On the fifth day bile ceased draining through the tube; and there was only slight drainage around the tube. Aspiration and manipulation of the tube loosened the obstruction with restoration of drainage. On the seventh day the bile became thin and pale, but excessive in amount (1260+ c.c. in twenty-four hours), the urinary output was 1590 c.c. Biliary drainage continued thin but gradually became reduced in amount. The blood urea on the eighth day was 34 mg. for each 100 c.c. On the ninth day the urinary output became less and remained so. The urine contained a moderate amount of albumin and many hyaline casts. On the tenth day the leukocytes were 34,000. The patient grew restless, then drowsy, and became progressively weaker until she died on the fifteenth day. There was a slight sanguineous discharge from the wound the last seven days.

Necropsy revealed a sinus passing down to the region of the common duct from which thick purulent material exuded. There was no generalized peritonitis, and very little gross hemorrhage in the region of the wound and none elsewhere. The heart and lungs were practically normal. The liver was small, weighing 985 gm., and its cut surface presented a brownish green mottling. The lobule markings were not distinct. The common and hepatic ducts were dilated. Microscopic examination revealed cells around the central veins shrunken in size, their shape irregular. In some lobules this condition extended out to the periphery. In the sinuses around the central vein was a moderate amount of brownish black pigment. The kidneys were atrophic, weighing, together, 185 gm. Microscopic examination showed moderate, cloudy swelling, areas of rather marked interstitial fibrosis, and many hyalinized glomeruli and atrophied tubules. There was considerable bile pigment. Death was attributed to nephritis complicated by lack of hepatic function.

Case 4 (A381682). Mrs. C. Z. W., aged forty years, presented herself for examination January 13, 1922, giving a history of recurring attacks of right upper abdominal pain without jaundice. Cholecystectomy had been performed elsewhere September 6, 1921. Shortly afterward jaundice developed, at first fluctuating, then persistently intense. The patient had lost considerably in weight.

The systolic blood pressure was 110, the diastolic 80. The pulse was 90. The hemoglobin was 69 per cent, the erythrocytes numbered 4,490,000. The coagulation time was eight minutes. The urine contained a moderate amount of albumin, and casts.

The preoperative preparation was begun January 15; 31 c.c. of calcium chlorid was given intravenously in four doses. The coagulation time of the blood was reduced to three minutes.

January 19, a hepaticoduodenostomy was performed because of the absence of the common duct. Marked biliary cirrhosis and an atrophic liver were noted. The patient did not react well after the operation. On the third day, the jaundice seemed to deepen, and weakness progressed. On the second day, the pulse rose to 110 and on the morning of the fourth day it became increasingly weak and rapid and the patient remained in syncope for three minutes. Vomiting of "coffee ground" material occurred often. There was moderate oozing from the wound the third night. The temperature was 98 the second and third days, falling shortly before death. Aside from marked cardiovascular asthenia the heart and lungs were negative. The urinary output was 240 c.c. the first day, 510 c.c. the second day, scanty the third day, and anuria developed the fourth day after operation. The urine contained a moderate amount of albumin but no casts. The blood urea before operation was 26 mg. for each 100 c.c. and the third day after operation, 68 mg. Death, which occurred on the fourth day, seemed to be due to general asthenia with insufficient hepatic function, complicated by moderate internal hemorrhage.

Only an incomplete necropsy could be obtained. There was less than 480 c.c. of blood in the abdomen. Microscopic examination of the liver revealed bile thrombi, atrophy of the liver cells around the central veins, and five granules of fat in the cells of the peripheral zone. Moderate fibrosis and lymphocytic infiltration occurred in the portal areas. The kidneys contained occasional sclerosed glomeruli and atrophic tubules with moderate swelling and granular change in the tubular epithelial cells. An excessive amount of bile pigment and many bile casts were present.

This is the only patient receiving preoperative preparation with calcium that had serious postoperative bleeding, and in this instance the bleeding seemed only contributory. The morning death occurred the coagulation time was twenty-one minutes and the calcium time twelve minutes.

Case 5 (A377643). Mr. E. G., aged fifty-seven years, presented himself for examination November 18, 1921. He had been perfectly well until February, 1919, when he had an attack of influenza, followed by increased thirst and polyuria. The urine contained sugar. No treatment was given. The patient began to lose weight and strength. May, 1921, pain and tenderness developed in the upper abdomen, and, in June, a mass in the epigastrium was discovered. The mass disappeared and symptoms were relieved, except for slight pain and jaundice which persisted. Six weeks before, jaundice had become more intense.

Examination revealed jaundice 2, pallor 1, and emaciation 1 to 2. The systolic blood pressure was 130, the diastolic 80; the pulse was 76. The patient's normal weight was 250 pounds, the present weight was 147 pounds. The specific gravity of the urine was 1.022; albumin 1, a trace of sugar and pus were found. The hemoglobin was 78 per cent. The erythrocytes numbered 3,980,000 and the leukocytes 5,000. The stools were clay colored and stercobilin was absent. The blood urea was 17 mg. for each 100 c.c. The blood sugar was 0.21 mg. The coagulation time was eight minutes.

The patient was sent to the hospital and received forced fluids and the diet for diabetic patients. The urinary output varied from 500 to 1,600 c.c. a day. The sugar disappeared from the urine. A transfusion was given of 500 c.c. of citrated blood November 29, and the next day the coagulation time was six minutes.

December 1, 1921, cholecystostomy was performed. Pancreatitis 4, biliary cirrhosis 3, and a hard nodule of the head of the pancreas were noted. White bile exuded from the dilated common duct. A profuse drainage of thin, pale bile followed the operation. The patient grew progressively worse after the fourth day. Pulse and heart sounds became feeble, and muscular weakness increased. The patient became drowsy, indifferent, and irritably restless. The urinary output was satisfactory throughout and remained sugar-free during his entire postoperative course. At no time was acetone present in the mrine. On the seventh day, the patient complained of pain under the right ribs radiating to the right shoulder. The leukocytes numbered 25,000. The vomitus was coffee ground in type and death occurred on the ninth day (Table 1).

At necropsy the liver weighed 2,550 gm., but showed marked central atrophy and hydropic change in the cells of the peripheral zones. The kidneys, together, weighed 413 gm. and revealed only moderate signs of nephritis. There was carcinoma of the head of the pancreas, miliary gastric ulcers, right adhesive pleuritis, and old endocarditis; coronary sclerosis and purulent seminal vesiculitis were the only other important pathologic changes.

The liver appeared to have been responsible for the death of this patient. Many surgeons have called attention to the seriousness of finding white bile at operation.[1, 2, 4] The discharge after operation contained some bile, but was chiefly seromucous.

In many instances in which the patients do not progress satisfactorily there is undoubtedly a combination of insufficient renal and hepatic function. Either may dominate the picture and their relative importance may change. Case 6 is of interest in this regard.

Case 6 (A379535). Mr. T. S., aged sixty-four years, presented himself for examination December 13, 1921. He had enjoyed excellent health until March, 1921, when he was taken ill with an attack of dizziness, weakness, and general malaise. In April, jaundice with clay-colored stools developed. His weight dropped from 235 pounds to 165 pounds in three months. The only pain was a dull ache in the posterior thoracic region and in both shoulders. He improved gradually from July to November, the jaundice remaining faint. November 24, jaundice again became deep, accompanied by malaise, loss of strength and weight. He passed from five to six frothy white stools a day.

Examination revealed intense jaundice, 3 to 4. The weight was 157 pounds, emaciation 2. The systolic blood pressure was 118, the diastolic 66. The pulse was 76. The urine contained a moderate amount of albumin and a few hyaline and granular casts. The hemoglobin was 66 per cent; the erythrocytes numbered 10,900.

The patient was sent to the hospital for preoperative preparation. The coagulation time of the blood was reduced from seven the three minutes by intravenous injection of 25 c.c. of 10 per cent calcium chlorid solution in three doses. The blood urea before operation was 24 mg. December 20, 1921, choledochostomy for choledocholithiasis was performed. Marked biliary cirrhosis and subacute pancreatitis were noted. The gall-bladder was contracted and did not contain stones. Drainage was instituted.

The postoperative course was satisfactory until the fifth day when the patient experienced a sharp pain in the abdomen radiating to the right shoulder. This was followed by slight deepening of the jaundice and slight decrease in the flow of bile. The blood urea was 60 mg. For the next six days there were increasing signs of uremia. On the eleventh day, the blood urea rose to 208 mg. The urine was loaded with hyaline and granular casts. The leukocyte count was 20,000. At the same time the blood showed a great quantity of bile macroscopically and the coagulation time was sixteen minutes. During the next few days the nephritis improved markedly. There was an excessive flow of very thin bile the twelfth and thirteenth days, and although the quantity was large the total amount of bile pigment seemed to be decreased. On the sixteenth day the blood urea was 128 mg. and there were only a few casts in the urine. The blood contained less bile and the coagulation time was eight minutes. Although the function of the kidneys seemed to be improving the patient became worse about the twelfth day. Weakness increased. The pulse and respiration grew more feeble. The patient became restless and indifferent. The bile drainage remained very thin, though less. Death occurred on the nineteenth day after operation. The urinary output had remained satisfactory throughout.

Necropsy revealed the liver to be firm and shrunken, and weighing 1,500 gm. There was a purulent discharge from the bile ducts. Microscopically, there were many bile thrombi in the capillaries of the central region; the hepatic cells were shrunken and distorted. There was moderate fibrosis of the portal areas with lymphocytic infiltration and a few polymorphonuclears. The combined weight of the kidneys was 325 gm. There were definite macroscopic and microscopic signs of nephritis.

Cumston, in a review of the conclusions of many French observers, Hélouin, Ramond, Géraudel, Sacquepée, Merklen, Lioust, and others, points out the fact that icterus may accompany acute nephritis with little or no manifestations of pathologic conditions in the liver. Azotemia is thought to be due to the renal insufficiency and to hyperfunction of the liver. In Case 6 the general picture was of clearing nephritis. The lowering of the blood urea was probably due to better elimination by the kidneys, and to diminished formation of urea, owing to lowered hepatic function.

Thus the patient with obstructive jaundice dies from hemorrhage, or renal or hepatic insufficiency. Hepatic insufficiency we believe differs from renal insufficiency; associated with the former there is abundant drainage of light colored bile, containing small amounts of the bile pigments. Patients become restless, then drowsy and stuporous, and finally succumb. During the entire course of the hepatic insufficiency little change occurs in content or volume of the urine, and the blood urea remains persistently low. Renal insufficiency is associated with the cessation of drainage of bile. But with the cessation of drainage, evidence is shown from day to day in the urine of a progressing nephritis, and anemia may increase in the last stages. During this period of renal insufficiency secondary to the damming back of the bile in the circulation, the jaundice deepens, the coagulation time of the blood lengthens, and the blood urea progressively ascends to the level of uremia.

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MALIGNANT NEOPLASMS OF THE GALLBLADDER AND EXTRAHEPATIC BILIARY DUCTS*

KINSLEY RENSHAW

The author reports studies on a series of 104 cases of malignant neoplasia of the extrahepatic biliary apparatus collected from the Mayo Clinic records between the years 1907 and 1921. For convenience this study is divided into two parts, (1) malignant neoplasia of the gallbladder, and (2) malignant neoplasia of the extrahepatic bile ducts.

MALIGNANT NEOPLASIA OF THE GALLBLADDER

From January, 1907, to January, 1921, 7,878 operations were performed for gallstones at the Mayo Clinic. Within this period primary malignancy of the gallbladder, confirmed by pathologic examination, occurred in eighty-four cases (carcinoma eighty-two cases, epithelioma one, and lymphosarcoma one). Carcinoma was divided into the adenomatous and colloid types, the adenomatous type being much more common and taking the form of papillary or ulcerative growths. In the series of eighty-four cases there were thirty-eight cholecystectomies and forty-six explorations; stones were present in a majority of instances.

Sixty-eight of the patients were females, and sixteen were males; in 75 per cent the disease occurred between the ages of fifty and seventy. Symptomatically, malignancy differs very little from other diseases of the gallbladder, and usually a differential diagnosis is impossible.

The 104 cases studied were divided into three groups:

Group 1.—Patients who begin to lose weight and strength rapidly after symptoms of gallstone colic for years; pain becomes continuous; jaundice, fever, and tumor may or may not be present.

Group 2.—Patients similar to those in Group 1, except that dyspepsia, instead of symptoms of gallstone colic, is present.

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Group 3.—Patients without symptoms up to one year before operation, then a sudden development of symptoms of malignancy, rapid loss of weight and strength, cachexia, and tumor. Jaundice may or may not be present. Some of these patients have pain, either of a dull boring character, or that of gallstone; others do not have pain.

The forty-six cases in which exploratory operations were performed are divided into three groups; thirty cases in Group 1; five cases in Group 2; and eleven cases in Group 3.

DISCUSSION

Twenty-nine of the thirty-eight patients on whom cholecystectomies were performed had had symptoms referable to the gallbladder for more than one year; nine had had symptoms for less than one year.

If the condition is operable cholecystectomy should be performed; cholecystostomy should only be performed when, besides the tumor, there is severe infection of the gallbladder, or as a path for the introduction of radium. Cholecystostomy for stones had been performed elsewhere in five of the eighty-four cases, indicating that malignancy may develop in gallbladders that have been drained.

W. J. Mayo considers jaundice as a contraindication to operation when a definite diagnosis of malignancy of the gallbladder has been made.

Complications may be due to perforation of the gallbladder, as in one case in the series, to empyema, or to extension to the neighboring viscus by continuity, contiguity, or metastasis.

Seven patients on whom cholecystectomies had been performed were alive six years after operation, a percentage of 8.3 cures. The diagnoses in these cases were: gallstones in three, gallbladder disease in three, and gastric carcinoma in one (in this case adhesions had developed between the gallbladder and the pylorus). The operative procedures were: cholecystectomy, excision of adjacent liver tissue, and choledochotomy in one; cholecystectomy and gastro-enterostomy in one (besides the malignancy there were gastric and duodenal ulcers).

CONCLUSIONS

1. Malignancy of the gallbladder is not an uncommon occurrence.

2. Carcinoma is the most common type of neoplasia found; sarcoma is exceedingly rare.

3. Gallstones are complications in a very large number of cases.

4. Heredity seems to have little influence in the development of malignancy in this organ.

5. Females and males are afflicted in the ratio of about four to one.

6. Seventy-five per cent of cases occur between the ages of fifty and seventy.

7. In most cases there has been a history of gallstones for some time.

8. Early cholecystectomy for stones will either prevent the development of malignancy or find the condition in its incipiency.

9. Later operation is of little value except as a diagnostic procedure.

MALIGNANT NEOPLASIA OF THE EXTRAHEPATIC BILIARY DUCTS

From 1907 to 1921, twenty cases of primary carcinoma of the bile ducts were confirmed by pathologic diagnosis at the Mayo Clinic. Eight were of the adenomatous type, two of the papillary type, and all with columnar, cuboidal, or spheroidal cells. Grossly, they varied from the annular constricting to the flat, diffuse, and, occasionally, villous type.

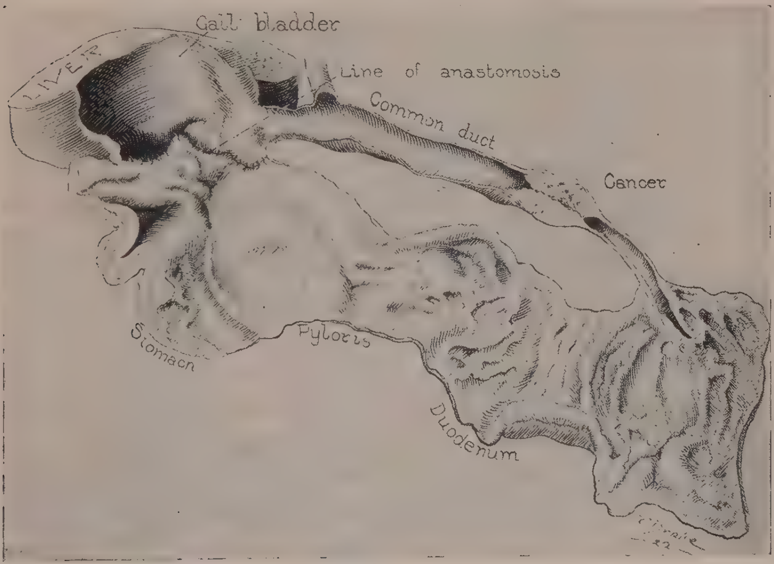

Fig. 24.—Cancer of the common duct; ducts dilated above. Cholecystogastrostomy.

The common duct was most often involved. In twelve cases the growth was in the common duct; in four it was at the juncture of the common and cystic ducts, two at the juncture of the common, cystic, and hepatic ducts, one at the upper end of the hepatic ducts, and one at the lower end (Figs. 24–28).

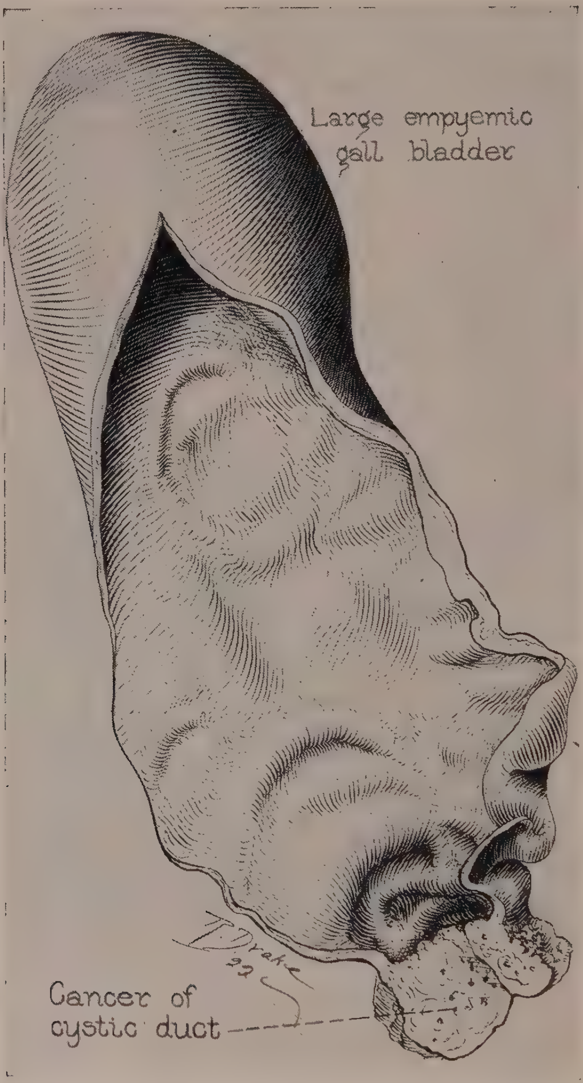

Fig. 25.—Cancer of the cystic duct with a large empyematous gallbladder.

In one specimen examined at necropsy the common duct was involved throughout the lower one-third. The hepatic duct was involved once, being associated with disseminated cancer of the intrahepatic bile ducts. The cystic duct was involved twice and the ampulla and papilla five times, one obstructing annular type of growth in the ampulla, and one involving the head of the pancreas.

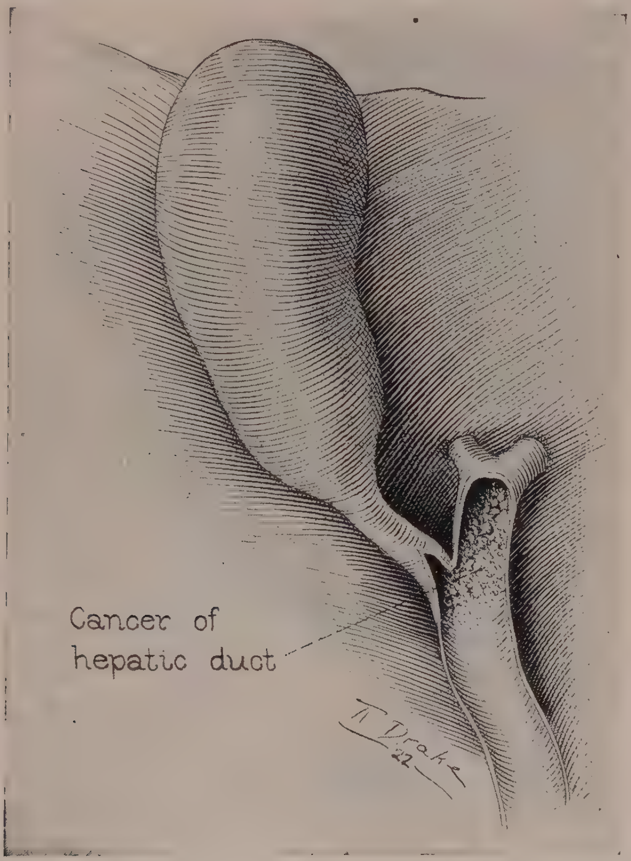

Fig. 26.—Cancer of the hepatic duct, probably originating at junction of hepatic and cystic ducts.

All but two of the twenty patients were operated on; three patients were explored; palliative operations were performed on eleven, and radical operations on four.

Stones were found in eight cases, stony material in two. Stones were found only in one of the five cases in which the growth was at the ampulla. Cancer of the hepatic duct was not associated with stones, while in both cases of cancer of the cystic duct, stones were present. Stones were present in five of the eleven patients with cancer of the common duct.

Thirteen patients were males and seven, females. The oldest patient was seventy-eight and the youngest, twenty-five.

The symptoms are usually those of obstructive jaundice, which, in about 50 per cent of the cases studied was preceded by or accompanied by a history of gallbladder or gallstone disease. Jaundice was a constant feature. Evidence of hemorrhage is important from a prognostic view and the diagnosis is as difficult, if not more difficult, than that of malignant conditions of the gallbladder.

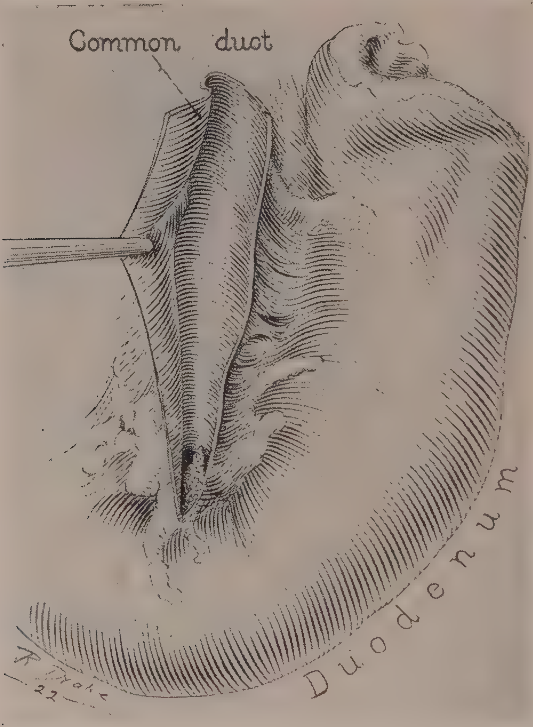

Fig. 27.—Extension of cancer of the ampulla and papilla up into the common duct. Duct dilated.

Of eighteen operations, three were explorations, eleven were palliative, and four were radical. Metastasis was found in four cases. The operative mortality of this series of cases (33.3 per cent) compares favorably with that reported by others. The average postoperative length of life of thirteen patients of the series was a little more than five months, one patient living fifteen months, and another a little more than three years.

The twenty cases of malignancy of the biliary tract were divided into four groups.

Group 1.—Cases in which there was a history of gallstone disease for a variable period, later associated with or followed by symptoms of obstructive jaundice.

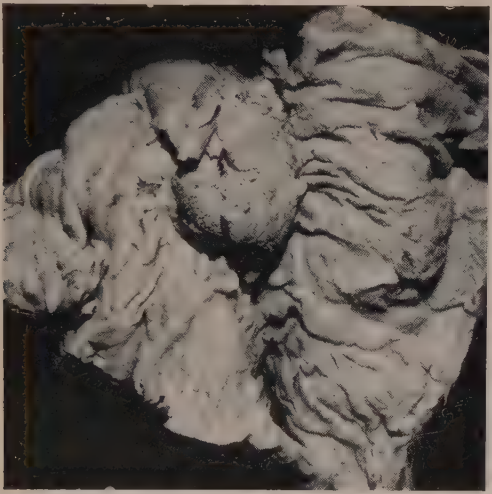

Fig. 28.—Carcinoma of the ampulla and papilla.

Group 2.—Cases in which the history of gallbladder disease was variable for a number of years, later associated with or followed by symptoms of obstructive jaundice.

Group 3.—Cases in which symptoms of obstructive jaundice developed, the insidious, painless type, or associated with pain.

Group 4.—Cases in which there was a history of diarrhea and pasty stools, of the pancreatitis type, followed later by symptoms of obstructive jaundice.

DISCUSSION

Surgical treatment of malignant conditions of the biliary tract has not advanced proportionately with that of other parts of the upper abdomen. Technical difficulties themselves do not seem to be responsible for this comparative tardiness.

Apparently the element that either prevents operation or causes failure, in a large percentage of cases, is hemorrhage. Recent clinical investigations on the control of hemorrhage in jaundiced patients by the intravenous administration of calcium have been carried out by Walters of the Mayo Clinic, and seem to advance some hope for better results in these cases. Certain preoperative and postoperative principles designed to conserve and stimulate the activity of the cells of the liver were recently reiterated and emphasized by Crile.

If it were not for hemorrhage, malignant conditions of the biliary ducts, being as a rule small, limited within the walls of the bile ducts, and late to metastasize, should lend themselves readily to surgical treatment.

CONCLUSIONS

1. Malignancy of the bile ducts, while less common than that of the gallbladder, is not uncommon. The ratio in a series of 104 cases of malignancy of the biliary ducts and gallbladder was one to four.
2. Carcinoma is the most common type of neoplasm found.
3. Gallstones would seem to be of greater etiologic importance than is generally considered.
4. Males and females are affected in the ratio of about two to one.
5. About two-thirds of the cases occur between the ages of fifty and seventy years.
6. A diagnosis of malignancy of the ducts is uncertain.
7. After a diagnosis of obstructive jaundice has been made, exploration is generally advisable.
8. From the standpoint of slowness of growth and rarity of metastasis, surgical treatment should be favorable.
9. Early treatment of disease of the gallbladder may occasionally prevent the development of malignancy.
10. Operation on patients with jaundice carries a high mortality.

ACCESSORY PANCREATIC TISSUE: REPORT OF TWO CASES*

EDMUND J. HORGAN

Eighty-one cases of accessory pancreatic tissue in man have been reported in the literature. In a series of 321 consecutive necropsies at the Mayo Clinic, in 314 of which the entire length of the intestine was opened, accessory pancreatic glands were found in two (0.6 per cent). In one case aberrant tissue was in the stomach; in the other, in the duodenum. In another instance pancreatic tissue was found at operation in the jejunum three inches from the ligament of Treitz and necessitated going below it to perform a gastro-enterostomy.

As a study of the embryology of the pancreas in the human has been possible only in a few instances, a comparative study of the anatomy and embryology is given. Oppel believes this organ is found in every species of vertebrate. The pancreas in man develops from buds of the duodenum as two anlages, while the number varies in different animals. The dorsal anlage begins as an outpouching of the duodenum and the ventral anlage as a grooved bud arising from the common bile duct at its origin with the duodenum. The growth of the former is more rapid than that of the latter. As the anlages grow they rotate around the inner aspect of the duodenum and meet posteriorly where coalescence takes place and development continues in one mass in the dorsal mesentery. The body and the tail grow upward and to the left so that they lie in the dorsal mesogastrium posterior to the stomach. As the stomach and dorsal mesogastrium change position the pancreas moves within the latter until its position is transverse, when it becomes fixed to the parietal peritoneum of the posterior abdominal wall.

The primitive outpouchings are lined with columnar epithelium which develops branching ducts. The main duct of the dorsal pancreas empties into the duodenum, while that of the ventral pancreas anastomoses with it. Thus, the duct of Wirsung arises from the main duct of the ventral pancreas and the distal half of the duct of the dorsal pancreas, while the duct of Santorini comes from the proximal duct of the dorsal pancreas.

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* Abstract of paper published in full in Archives of Surgery, 1921, ii, 521–534. From the Section on Surgery, Mayo Clinic.

At the end of the branches of the main duct the tubules have an enlarged bud which develops into acini and the islet cells then appear in the connective tissue along the small ducts. The connective tissue is derived from the mesodermal tissue of the dorsal mesentery.

From the surgical standpoint it is logical that the abnormal position of aberrant pancreatic tissue predisposes to inflammation and malignancy. It is possible that carcinoma of the duodenum, which is occasionally observed, originates in accessory pancreatic tissue. This type of tissue has been found to be the cause of intussusception and also of diverticula of the duodenum following inflammation in the aberrant structure. Extension of the inflammatory process has produced bands and loopholes which later caused obstruction and strangulation.

There is no accepted theory as to the cause of accessory pancreatic tissue. Zenker believes it due to an anomalous formation of an additional diverticulum of the duodenum, and Glinski attributes it to a failure of one of the primitive anlages to coalesce with those of the main pancreas. This cannot be accepted, however, because the aberrant masses are small and are not confined to the duodenum; they have been found in the stomach, duodenum, jejunum, ileum, spleen, omentum, and so forth. The author believes that they are due to branching buds which come in contact with and are then engrafted on the various viscera in the process of their development. The size to which accessory pancreatic tissue grows is in proportion to the normal capabilities of development of the bud which is engrafted in the abnormal situation and of the new environment.

CARCINOMA OF THE APPENDIX*

ARNOLD S. JACKSON

Carcinoma of the appendix will often be overlooked, unless a careful routine examination is made of all appendixes removed. Suspicion is cast on the obliterated, or partially obliterated, harmless-appearing type because it has been shown that one in every fifty-three of these is carcinomatous.

In two series totalling 8,039 appendixes which were examined microscopically by MacCarty and MacGath at the Mayo Clinic forty were found to be carcinomatous. In order to determine the prognosis the author has followed these forty cases in addition to twenty-four subsequent ones. The total number of cases found in the literature with the twenty-four here reported is 317.

Thirty-seven of the sixty-four patients observed in the Clinic were traced. Two had died from accidents or conditions in no way related to the disease and two had died from postoperative complications. The remaining thirty-three are living and, in most instances, well. Twelve were well ten to sixteen years after operation; ten, five to ten years, and two, one to five years. The malignancy was cured in 100 per cent of the patients traced. In only five of the sixty-four cases was a positive surgical diagnosis made of carcinoma, and the lesion was suspected in four other cases.

The consequences of failure to recognize the condition and remove the tumor cannot be stated because the possibility of carcinoma of the large bowel originating in the appendix is an unsettled question, but it must be considered.

There is little of significance in the clinical history of these cases. Fifty per cent of the patients gave a history of previous trouble. The disease is seen twice as often in women as in men. The process should be carefully examined in all patients with a history of previous trouble in the appendix because many malignant appendixes may thus be discovered which may otherwise be overlooked.

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* Abstract of paper published in full in Archives of Surgery, 1923, vi, 633–660. From the Section on Surgery, Mayo Clinic.

In the twenty-four cases reported by the author the carcinoma occurred at the tip in twenty-one, at the base in two, and at the middle in one. The tumor in situ grossly resembles concretions within the lumen. On transverse section the lumen is seen to be obliterated by a solid growth which is homogenous and fibrous in appearance and presents an orange color in specimens preserved in formalin.

Considerable doubt exists as to the pathology of these tumors. Graham divided them into two main groups, the spheroidal cell carcinoma and adenocarcinoma. In his series 73.8 per cent of the cases were of the spheroidal type. Adenocarcinoma occurs later in life than the spheroidal type and corresponds more closely to the age at which carcinoma of similar type occurs in the large intestine. Adenocarcinoma is the more malignant; the spheroidal type rarely invades the cecum or spreads by metastasis to the abdominal glands. Prognosis will, therefore, depend largely on the type of cell of which the tumor is composed.

The microscopic picture is that of irregular masses of epithelial cells closely packed in alveoli surrounded by heavy fibrous stroma. The growth is confined chiefly to the mucous and submucous layers. The protoplasm of the cells is pale and scanty, but the nuclei stain darkly and are generally oval or round with fewer irregularities than are presented by carcinomatous cells in other portions of the alimentary canal. In this series of sixty-four cases one was diagnosed colloid carcinoma, the remainder belonging to the spheroidal type. Adenocarcinoma was not found.

Chronic inflammation as a factor in the production of carcinoma is evident from a study of the specimens. An analogy exists in the development of gastric cancer on an ulcer basis.

The author concludes that a preoperative diagnosis of carcinoma of the appendix is impossible, because of the absence of distinguishing clinical signs. The prognosis following early removal of carcinoma of the appendix is more favorable than for malignancy in any other part of the gastro-intestinal tract. There is a definite relationship between chronic inflammation and carcinoma of the appendix. The appendix should be examined carefully whenever the abdomen is opened and should be removed if at all suspicious. The relationship of cecal carcinoma to carcinoma of the appendix has not been proved.

DILATATION OF THE COLON SIMULATING HIRSCHSPRUNG'S DISEASE*

JAMES A. H. MAGOUN, Jr.

Hirschsprung divided cases of Hirschsprung's disease into two types, true megacolon occurring in infants, and pseudomegacolon occurring in adults. Magoun classifies them into three groups:

1. The congenital type or true Hirschsprung's disease: (a) that occurring in infancy or early life, (b) that in which obstinate constipation, abdominal distention, and emaciation have been present since birth, but the patient has reached adult life.

2. Cases in which chronic constipation has been present for years and the symptoms of Hirschsprung's disease developed within a short period without demonstrable mechanical obstruction.

3. Cases of megacolon due to mechanical obstruction, such as (a) those occurring in infancy and due to atresia or stenosis of the rectum, (b) those occurring in adult life and due to tumors, volvulus, adhesions, inflammatory stenosis, or external pressure on the bowel.

The author reports the case of a man thirty-six years of age which falls into the last group, the cause being a carcinomatous papilloma in the first part of the descending colon. Although the patient was constipated from childhood, obstinate constipation had been present for only two years. During this period he had complained of occasional cramp-like pains. The roentgen ray demonstrated a dilated colon. At the first operation a modified Brown technic was used. At the end of five months the patient had gained 35 pounds and was free from pain. At a second operation the lower portion of the ileum, the cecum, appendix, and the colon to a point below the growth were removed and the ileum and colon joined by end-to-end anastomosis. Convalescence was uneventful.

The pathologic findings in this case were similar to those of true Hirschsprung's disease and, in addition, there was a carcinomatous papilloma of the ring type. The muscular layers of the colon were markedly hypertrophied.

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* Abstract of paper published in full in Surgery, Gynecology, and Obstetrics, 1922, xxxiv, 198–200. From the Section on Surgery, Mayo Clinic.

THE INVOLVEMENT OF THE LYMPH GLANDS IN CARCINOMA OF THE LARGE INTESTINE*

JAMES M. HAYES

Carcinoma is more common in the large intestine, with the exception of the stomach and possibly the rectum, than in any other part of the alimentary tract, according to statistics reported by DeBovis, Brill, Hemmeter, and Nothnagel. W. J. Mayo found that of 1,264 cases of carcinoma of the gastro-intestinal tract, in which operation was performed at the Mayo Clinic between October, 1897 and November, 1911, 863 involved the stomach, fourteen the small intestine, 219 the large intestine, and 168 the rectum.

Carcinoma of the large intestine begins in the crypts or glands of Lieberkühn. The epithelium of the degenerated mucous glands then perforates the muscularis mucosa and the deeper tissues of the intestinal wall. The involvement of the lymph glands may take place as soon as the process reaches the lymphatic network of the submucosa, or it may take place through the intermuscular lymphatic network. Metastasis usually develops very slowly in carcinoma of the large intestine.

Extension may be direct, by the lymphatics, and by the way of the portal vein and its tributaries. W. J. Mayo calls attention to traumatic dissemination of malignant disease, especially during operation. He believes that the infected thrombi in the derivatives of the portal vein are loosened and carried to the liver.

One hundred preserved specimens which had been removed at operation at the Mayo Clinic furnish the basis of this study. Forty-two per cent of the patients were in the sixth decade. The average age was fifty-two and three-tenths years; the youngest was twenty-one and the oldest seventy-six. Fifty-one were males and forty-nine were females. Fourteen hundred six glands were obtained from the 100 specimens, an average of fourteen and six-hundredths glands for each specimen. In 63 per cent metastasis had not occurred; in 37 per cent one or more glands were involved. Very few specimens contained more than two or three involved glands. All cases were classified in two groups. In Group 1 were cases of carcinoma of the large intestine without metastatic involvement of the regional lymph glands, and in Group 2 were cases of carcinoma of the large intestine with metastatic involvement of one or more regional lymph glands.

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* Abstract of paper published in full in Minnesota Medicine, 1921, iv, 653–663. From the Section on Surgical Pathology, Mayo Clinic.

A study of these two groups suggested another division, Group 3, in which were placed cases of colloid carcinoma of the large intestine, those without metastatic involvement of the regional lymph glands, and those with involvement of the lymph glands.

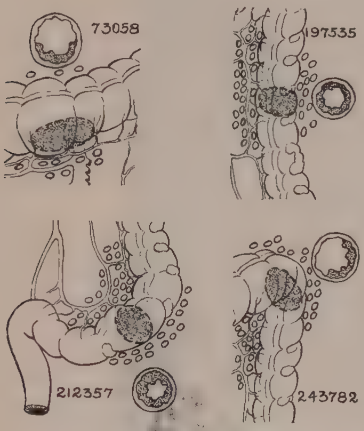

Fig. 29.—Group 1. Diagrams showing relative positions of glands and growths. The circles represent glands not involved.

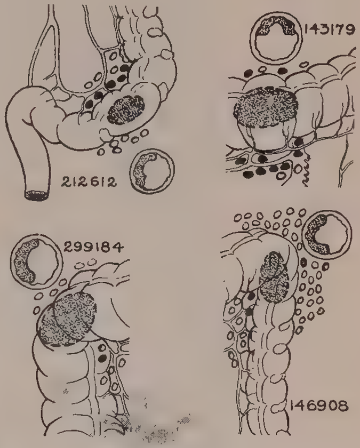

Fig. 30.—Diagrams showing relative positions of glands and growths. The black circles represent glands involved.

There were sixty-three patients in Group 1, thirty-one females and thirty-two males. While there were several specimens in which few or no glands could be found, there were many large glands in the majority. Representative diagrams of the glands and growths are shown in Figure 29. McVay pointed out that the size of the malignant growth in the rectum bears no relation to the glandular involvement. My study proved the same rule. This type of carcinoma had large protuberant growths from the walls of the intestines that extended into the lumen causing more or less obstruction. The encircling form of carcinoma was present in twelve of the sixty-three patients.

There were thirty-seven patients in Group 2, nineteen males and eighteen females. The average duration of symptoms was ten and six-tenths months. The average number of glands in each specimen was sixteen and seventy-five hundredths. The number of glands involved in each case varied from one to thirteen. Representative diagrams of the glands and growths are shown in Figure 30. The size of the growth bears little or no relation to the amount of glandular involvement, and the glands usually involved are those nearest the point of greatest direct extension of the growth.

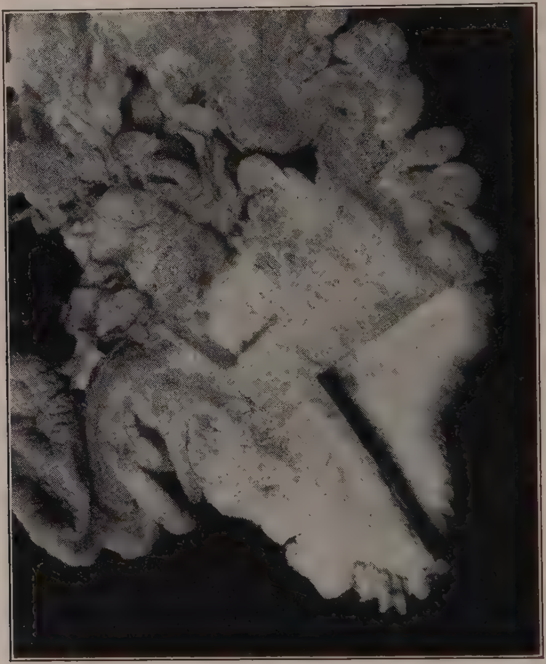

Fig. 31.—Group 1. Growth protruding into the lumen of intestine, but not extending into the intestinal wall.

Figures 31 and 32 show typical specimens of the growths in Group 1 and Group 2 respectively. In Group 1 the growth projects into the lumen, while in Group 2 it tends to extend into the muscle and fatty tissue surrounding the bowel, and often extends to and involves other organs, such as the bladder, ovary, and uterus. The ulcerative type of growth is more common in Group 2.

There were eight patients with colloid carcinoma without metastatic involvement of regional lymph glands, five females and three males. Clinically, most of the patients of this group showed very mild malig-

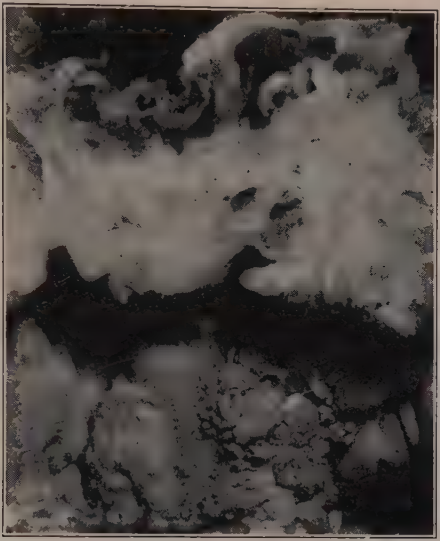

FIG. 32.—Group 2. Extensive involvement of the intestinal wall and slight projection into the intestinal lumen by carcinoma.

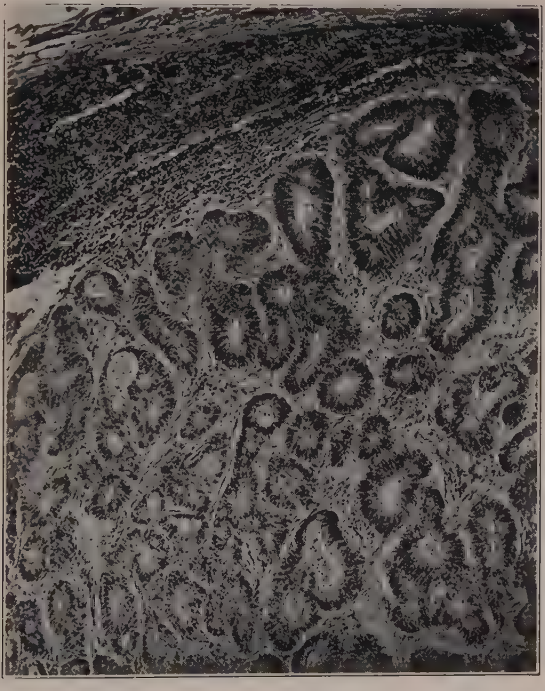

FIG. 33.—Extensive carcinomatous involvement of lymph gland with a marked tendency to cell differentiation.

nancy. There were eight patients with colloid carcinoma with metastatic involvement of regional lymph glands. The average duration of symptoms was sixteen and one-tenth months. The average number of glands involved was four and five-tenths. Some of the most malignant cases, clinically, were in this small group.

Ninety-five glands obtained from the 100 specimens showed metastatic involvement, thirty-nine (41 per cent) were found in patients with colloid carcinoma with metastatic involvement of the lymph glands.

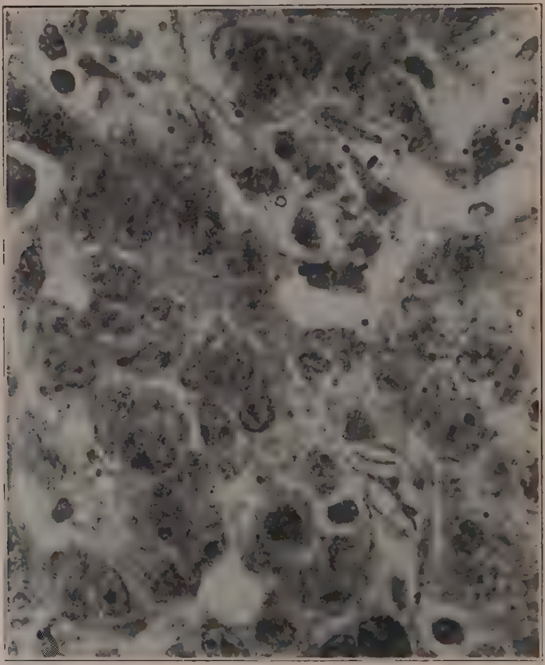

Fig. 34.—Metastasis in lymph gland with very little tendency to cell differentiation. Large "one eyed" carcinoma cells; some mitotic figures.

Five of nineteen cases with evidence of recurrence in one and one-half years were in this group.

Clogg believes that carcinoma of the large intestine is often a local disease. MacCarty and Broders have called attention to the fact that, if the cells in metastasis from carcinoma are differentiating, the carcinoma tends to limit itself. Figure 33 shows extensive metastasis in a lymph gland with advanced cell differentiation. The tendency to gland formation is evidence of cell differentiation. A marked contrast to this is shown in Figure 34, in which very little cell differentiation, but marked destruction of tissue, is visible. Beginning metastasis in a large lymph gland is illustrated in Figure 35. The involvement is first evident near the periphery of the gland through the lymph sinuses. This has been pointed out by Billroth, MacCarty and Blackford, Zehnder, and McVay.

The statement has often been made that of growths of the entire alimentary tract, those of the large intestine have the lowest degree of malignancy. MacCarty and Blackford found glandular involvement in 52 per cent of 200 cases of carcinomas of the stomach; McVay found glandular involvement in 47 per cent of carcinomas of the rectum. In this series metastasis was found in only 37 per cent.

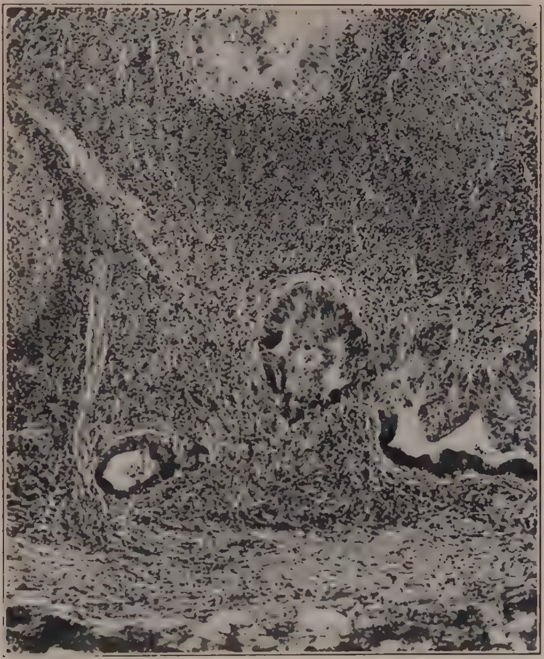

FIG. 35.—Early metastasis in a lymph gland.

In the 100 patients of this series, the sigmoid flexure was involved in forty-two, the descending colon in twenty-one, the splenic flexure in seven, the transverse colon in sixteen, the hepatic flexure in nine, and the ascending colon in five.

CONCLUSIONS

1. Carcinoma of the large intestine occurs most commonly in the sixth decade, but it is quite common from the third decade on; it occurs about equally in both sexes.

2. Carcinoma of the large intestine metastasizes less often than carcinoma of any other part of the gastro-intestinal tract.

3. In the series of 100 cases metastasis occurred most often in the sigmoid flexure, and in the other parts in the following order: descending colon, transverse colon, hepatic flexure, splenic flexure, and ascending colon.

4. Carcinomas without local metastasis usually protrude into the lumen rather than penetrate the walls of the intestine.

5. Carcinomas with local metastasis usually extend into the wall of the intestine rather than into the lumen.

6. Metastasis may occur in the liver without a sign of local metastasis.

7. Colloid carcinoma metastasizes and is often present in the most highly malignant cases.

8. Lymph glands may be only inflammatory, but with such marked cellular infiltration and lymphedema as to simulate large carcinomatous glands, both in size and consistency.

9. Very small glands, too small to palpate under ordinary conditions in the abdomen, may be carcinomatous.

10. The size of the growth is no criterion of the presence or absence of metastasis.

11. Only by a systematic microscopic examination is it possible to rule out local metastasis in carcinoma of the large intestine.

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INVOLVEMENT OF THE LYMPH NODES IN CARCINOMA OF THE RECTUM*

JAMES ROBERT McVAY

The rectum next to the stomach is the most common location for malignant disease in the gastro-intestinal tract. Mayo reported 561 cases of malignant disease of the gastro-intestinal tract seen in the Mayo Clinic in 1908 and 1909. Of these growths 387 were in the stomach, three were in the small intestine, sixty-nine were in the large intestine, and ninety-two were in the rectum. Gant, Ball, and Halstead assert that rectal cancers make up about 4 per cent of all the cancers of the body, and that about 80 per cent of the intestinal cancers occur in the rectum.

Patients with cancer of the rectum are usually in the sixth decade but they may be any age. W. J. Mayo, in 120 operative cases, found the average age to be fifty-two years. Oehler, discussing the cases in Kraske's Clinic, says the average age is fifty-six years, slightly higher in males than in females. He quotes Kupferle in Czerney's clinic who reported a case of rectal carcinoma in a patient aged thirteen years and the Rostocker Clinic as having two cases in patients fourteen and fifteen years respectively.

The disease is more common in males than in females. In 25,000 cases of disease of the rectum treated for fistula reported from St. Mark's Hospital by Edwards, 775 were malignant. Five hundred forty-two of the patients were males and 233 were females. In Lynch's 491 cases there were 281 males and 210 females.

The duration of symptoms is usually under one year. Lynch found it to average eight months in 491 cases; in 20 per cent it was from nine to twelve months.

Various writers fail to agree on the location of the growths. Cole gives the favorite site as the anterior and lateral walls; Rawling believes that the posterior wall is most often affected, and Oehler says that they occur as often on the anterior as on the posterior wall. Edwards asserts that about 80 per cent of the growths occur 5 to 7.5 cm. from the anus, Gant, in 100 cases, found 50 per cent in the ampulla and 15 per cent in the upper rectum and sigmoid, while W. J. Mayo in 100 consecutive cases found 63 per cent in the rectosigmoid, 30 per cent in the rectum, and 7 per cent in the anal canal. Mummery believes the commonest site is the rectosigmoid, and next the ampulla. He believes that those who say the growths occur at a lower level do not take into account the fact that they may descend after starting.

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery, May, 1920. Reprinted from Annals of Surgery, 1922, lxxvi, 755–767. From the Department of Surgery, Mayo Clinic.

The usual type of growth is adenocarcinoma. In Lynch's 491 cases, 451 were adenocarcinomas. Of Gant's 100 cases, 95 per cent were cylindric carcinomas and in three-fourths of the cases studied by Oehler, the growths were of the type which he calls adenocarcinoma simplex. In view of the various classifications which have been given to carcinomas of the rectum, some based on clinical grounds, others on histologic grounds, and still others developed from a combination of both, it seems best not to attempt any classification other than carcinoma.

Carcinoma of the rectum develops from the crypts or glands of Lieberkühn which when they take on their migratory activities break through the tunica propia of the mucosa into the submucosa, invade the circular muscular coat and, on reaching the intermuscular lymphatic network, tend, according to Cole, to progress around the bowel in the direction of these vessels. This accounts for the encircling tendency of rectal carcinoma. From here the cells invade the longitudinal muscle layer and on reaching the outer muscle wall their extension is restricted by the rectal fascia. The invasion of the lymph nodes through the lymphatics may occur at any time after the disease reaches the submucosa but such invasion is usually late. W. J. Mayo says that more cases are inoperable because of local extension than because of metastasis. Three methods of extension are described by Miles: downward into the wall of the bowel below the growth, into the rectal sphincter, and ischiorectal fossa; lateralward into the fascia propia, levator ani muscles, capsule of the prostate, seminal vesicles, and base of the bladder in the male, and the vaginal wall and genital organs in the female, and upward into the bowel above the growth, and the pelvic peritoneum and mesocolon. Handley has described a marked dissemination in the submucosa occuring early. This he claimed to have demonstrated by mucicarmin staining of entire sections of the bowel.

Cole, Monsarrat and Williams, and Cheatle were unable to confirm his findings.

Cancer of the rectum metastasizes slowly in most cases. Oehler had fifty-eight patients die from carcinoma of the rectum and thirty-four had no internal metastasis. Zinner found metastatic enlargement of retroperitoneal lymph nodes in only 3.5 per cent of the 141 patients examined. Pennington collected data on 997 necropsies of patients dying from cancer of the rectum and in 324 the regional nodes were found to be involved. Metastasis when it does occur usually takes place in the liver. Oehler says that metastasis is most frequent in the liver and retroperitoneal lymph nodes and that the lungs are seldom involved, and the remaining organs still more seldom. Rectal carcinoma may reach the liver through glandular metastasis or by the breaking off of emboli of carcinoma cells into the portal circulation, a method recognized and described by W. J. Mayo, McArthur, Smith, and others.

MATERIALS AND METHODS

One hundred specimens were studied which had been removed at operation at the Mayo Clinic. The size, location, form, extent, and character of the growth were studied as well as the normal mucosa, skin, surrounding fat, and fascia. Photographs were then made of the specimens, one showing the growth from the mucosal side, and one showing a cross section cut through the center of the growth in the longitudinal axis of the bowel. The character and extent of the invasion of the growth into the submucosa, muscular coats, glands, fat, and fascia were studied and sketches of the specimens were made, showing the relative location and size of the growth recorded in millimeters.

The anorectal lymph nodes were then carefully dissected out, and as each gland was removed its location in the longitudinal and radial directions was recorded on the sketch. The glands were then placed in small phials correspondingly numbered and preserved in formalin. A section of the original growth was also made and similarly preserved. Frozen sections averaging about 10 microns in thickness were made of each gland and these were stained in hemotoxylin and eosin and mounted in balsam.

The sections of the glands were studied for metastasis. On the sketches the results of the microscopic examinations were recorded for each gland with appropriate notes of any striking features.

The results were then recorded on printed diagrams. The diagrams were made to represent the sigmoid, rectum, and anus as viewed posteriorly and also the rectum in cross section. The growth was sketched in its relative position and the lymph nodes were placed as near as possible in the relative position in which they were found. Glands which showed no carcinomatous involvement on microscopic examination were represented as clear circles, while those showing metastatic involvement were represented in solid black. The variation in the size of the glands is not indicated in the diagram.

RESULTS

Forty-seven per cent of the patients were in the sixth decade and 96 per cent were between thirty-one and seventy years (Table 1). The average age was fifty and eighty-eight hundredths years. The youngest were two patients twenty-nine years and the oldest was seventy-nine. There were fifty-seven males and forty-three females. The average duration of symptoms was ten and four-tenths months.

TABLE 1

Distribution in Decades of the 100 Cases of Carcinoma of the Rectum

Age.	Patients.
21 to 30 years (29, 29, 30)	3
31 to 40 years	12
41 to 50 years	22
51 to 60 years	47
61 to 70 years	15
71 to 80 years (79)	1
Total	100

Six hundred twenty-three glands were obtained from the 100 specimens, or an average of six and twenty-three hundredths glands for each specimen. Fifty-three per cent of the specimens did not show glandular involvement, 30 per cent showed slight glandular involvement, and 17 per cent showed marked glandular involvement. The cases may be readily classified into three groups: Group 1, cases of carcinoma of the rectum without metastatic involvement of the regional lymph nodes; Group 2, cases of carcinoma of the rectum with metastatic involvement

TABLE 2

GROUP 1. CASES OF CARCINOMA OF THE RECTUM WITHOUT METASTATIC INVOLVEMENT OF THE LYMPH NODES

Case.	Sex.	Age.	Duration of symptoms, months.	Glands dissected out.	Case.	Sex.	Age.	Duration of symptoms, months.	Glands dissected out.
669–½J	F.	50	(?)	6	A120405	F.	47	12	10
A2252	F.	53	5	2	A121876	M.	54	15	6
A3663	F.	34	11	2	A123863	F.	61	12	10
A7676	F.	46	6	10	A124529	M.	55	24	11
A7769	M.	42	4	8	A132394	M.	55	18	4
A8928	F.	41	3	6	A136043	M.	69	24	7
A715	F.	58	12	5	A138027	F.	51	4	3
A1484	F.	53	36	5	A142982	F.	47	36	1
A6354	F.	54	8	3	A147264	F.	67	3	2
A25364	F.	61	12	2	A148799	M.	69	5	11
A26283	F.	70	(?)	6	A154180	M.	34	12	4
A43441	F.	57	12	9	A157347	M.	54	12	7
A47322	F.	53	18	10	A163565	M.	43	24	10
A57201	F.	51	10	9	A170796	M.	57	8	4
A68756	M.	51	12	1	A179420	M.	48	36	9
A70580	F.	56	3	7	A189827	M.	55	11	7
A70730	M.	53	12	5	A198743	F.	53	3	4
A81871	M.	52	7	4	A200441	F.	38	5	6
A97023	M.	60	18	3	A204879	M.	57	13	9
A100372	M.	50	12	12	A208438	M.	44	3	5
A102258	M.	45	6	5	A212669	F.	40	24	5
A103155	M.	64	12	6	A216300	M.	39	9	4
A104886	M.	46	8	11	A216842	M.	43	7	7
A107782	M.	44	4	4	A215439	M.	51	12	4
A111786	M.	50	12	10	A251281	M.	54	3	5
A113133	F.	51	12	9	A250263	M.	54	7	2
A113219	M.	53	12	6					

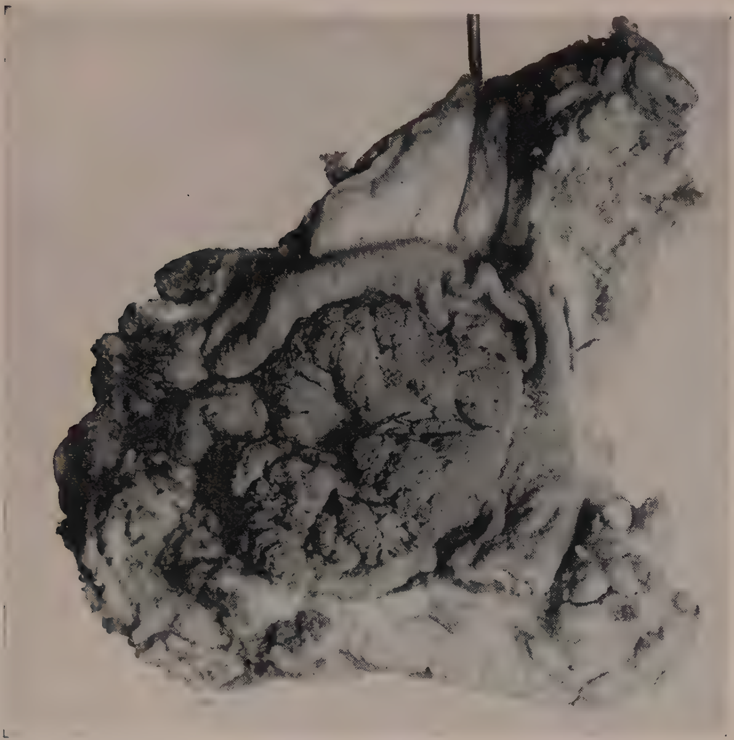

FIG. 36 (Case A100372).—Typical specimen of Group 1.

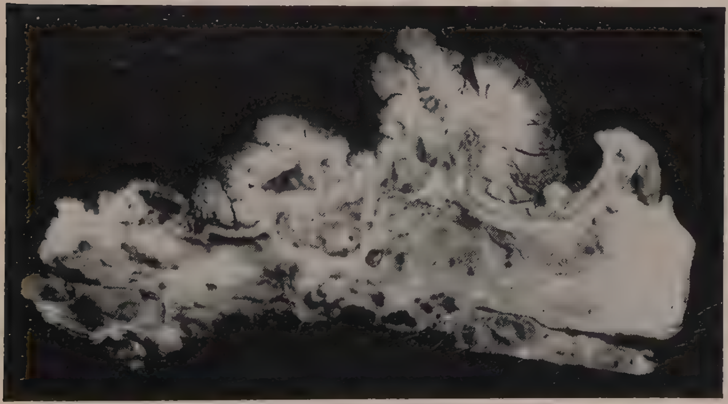

FIG. 37.—Longitudinal section of the growth shown in Fig. 36.

of less than one-half of the regional lymph nodes, and Group 3, cases of carcinoma of the rectum with involvement of one-half or more of the regional lymph nodes.

Group 1.—This group contained fifty-three patients (53 per cent). Thirty were males and twenty-three were females. The average age was fifty-one and six-tenths years. The average number of glands for each specimen was six and nine-hundredths (Table 2).

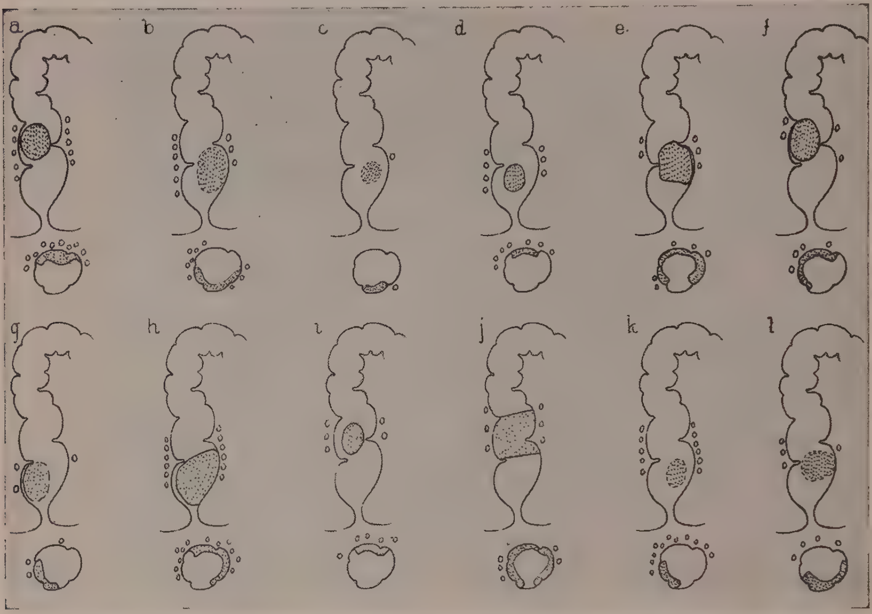

Fig. 38.—Diagram of relative position of glands and growth in twelve cases of Group 1. Glands not involved are shown as clear circles; glands involved are shown in solid black. a (Case A47322). Growth measuring 50 by 50 mm.; 10 cm. from anus. b (Case A57201). Growth on anterior wall measuring 50 by 70 mm.; 5 cm. from anus. c (Case A68756). Growth on anterior wall measuring 15 by 20 mm.; 5 cm. from anus. d (Case A70580). Growth on posterior wall measuring 25 by 33 mm.; 3 cm. from anus. e (Case A70730). Growth on posterior wall measuring 45 by 45 mm.; 6 cm. from anus. f (Case A81871). Growth on left and posterior wall measuring 40 by 50 mm.; 10 cm. from anus. g (Case A97023). Growth on anterior and left wall measuring 30 by 35 mm.; 3 cm. from anus. h (Case A100372). Growth on posterior and right wall measuring 50 by 70 mm.; 2 cm. from anus. i (Case A102528). Growth on posterior wall measuring 30 by 53 mm.; 10 cm. from anus. j (Case A103155). Encircling growth measuring 70 by 70 mm.; 10 cm. from anus. k (Case A104886). Growth on left and anterior wall measuring 20 by 25 mm.; 4 cm. from anus. l (Case 107782). Growth on anterior wall measuring 60 by 35 mm.; 4 cm. from anus.

One of the most striking features is that the size of the growth (Figs. 36 and 37) apparently bears no relation to the extent of glandular involvement (Fig. 38). Most of the growths in this series were above the average in size and caused symptoms of equal or longer duration than

TABLE 3

Group 2. Cases of Carcinoma of the Rectum with Metastatic Involvement of Less Than One-half of the Lymph Nodes

Case.	Sex	Age.	Duration of symptoms, months.	Glands dissected out.	Glands involved.
A19499	M.	36	3	3	1
A26781	F.	52	7	3	1
A43021	F.	30	12	7	2
A44196	M.	66	2	9	1
A47912	M.	39	12	7	1
A64157	M.	29	36	5	1
A66903	F.	53	10	7	1
A69046	M.	59	9	8	2
A69290	M.	66	12	6	1
A73143	F.	68	3	9	2
A79532	M.	48	24	7	1
A80562	M.	56	1.5	8	1
A99562	F.	45	6	5	2
A101064	F.	53	9	5	2
A109751	F.	59	10	7	1
A159369	F.	38	24	8	1
A164471	F.	58	18	8	3
A166175	M.	50	2	7	2
A168277	F.	52	5 (?)	5	2
A169130	M.	58	12	11	3
A169140	F.	56	24	6	1
A174098	M.	42	18	7	1
A174591	M.	60	12	6	1
A176669	M.	51	12	9	2
A185201	F.	40	12	10	3
A187873	M.	59	9	5	1
A201505	F.	51	12	4	1
A250973	M.	79	3	4	1
A2360	M.	63	8	5	1
A5092	M.	56	6	6	1

the average for the series. Most were protuberant and appeared to be growing into the lumen of the bowel rather than into the bowel wall as is seen in the cross section of the growth. Little attempt at direct extension into the muscle and fatty layers is seen. The glands vary in size; many were much larger than those in the other groups, so that no

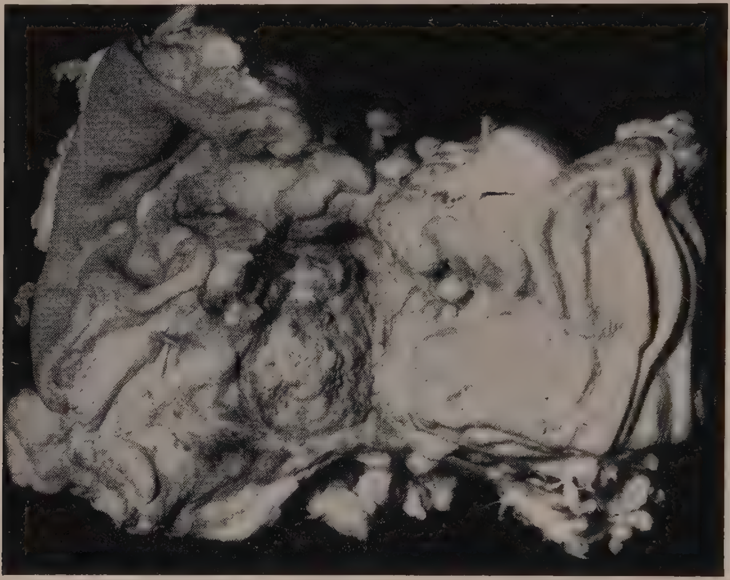

FIG. 39 (Case A176669).—Typical specimen of Group 2.

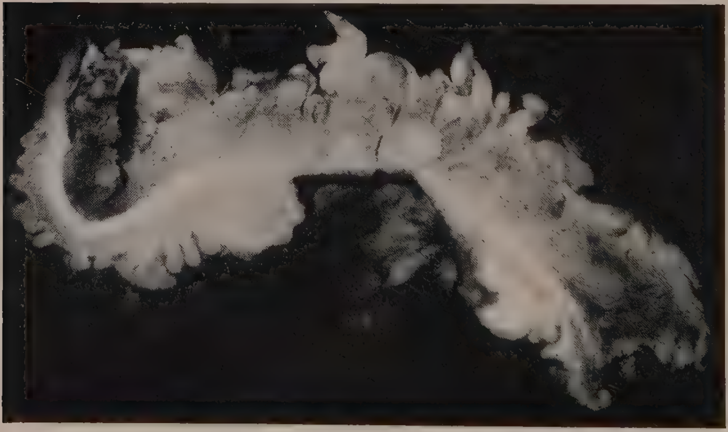

FIG. 40.—Longitudinal section of the growth shown in Fig. 39.

attempt was made to demonstrate the relative size of the glands on the diagrams.

Group 2.—There were thirty patients (30 per cent) in this group. Seventeen were males and thirteen were females. The average age was forty-eight and six-tenths years and the average duration of symptoms was eleven and one-tenth months. The average number of glands for each specimen was six and five-tenths. The sex, age, duration of symptoms, number of glands found, and number of glands involved in each specimen are shown in Table 3.

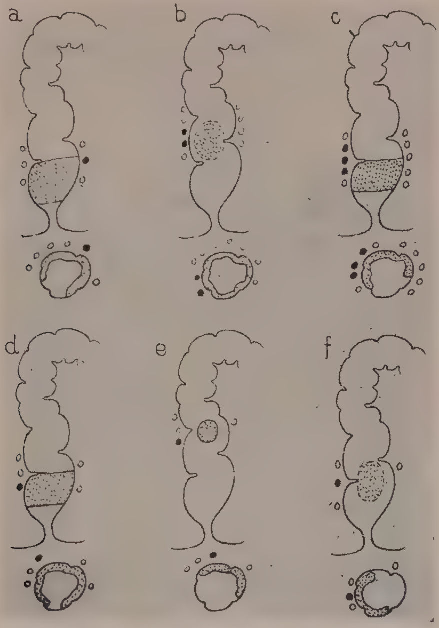

FIG. 41.—Diagram showing relative position of glands and growth in six cases of Group 2. Glands not involved are shown as clear circles; glands involved are shown in solid black. a (Case A174591). Growth on anterior wall measuring 95 by 60 mm.; 3 cm. from anus. b (Case A176669). Encircling growth measuring 50 by 60 mm.; 6 cm. from anus. c (Case A185201). Encircling growth measuring 45 by 40 mm.; 7 cm. from anus. d (Case A187873). Encircling growth measuring 80 by 55 mm.; 3 cm. from anus. e (Case A201505). Growth on posterior wall measuring 20 by 20 mm.; 12 cm. from anus. f (A250973). Growth on left wall measuring 50 by 50 mm.; 9 cm. from anus.

The photographs of this group (Figs. 39 and 40) also show that the size of the growth bears no direct relation to the amount of glandular involvement (Fig. 41). The protuberant type of growth occurred less often; most of the growths showed excavated ulcers. The growths showed a tendency to grow into the muscular tissue and the fatty tissue around the bowel wall, and thus to disseminate by direct extension. The gland or glands usually involved are those nearest the point of greatest direct extension. In other words, the metastasis is slow and the microscopic pictures show that the majority of the cells in most of the affected nodes as seen in Figure 42 reach the state of secondary cytodifferentiation.[11] In many of the involved glands the cells are arranged in acinar form and in some this differentiation is advanced to the point of mucous production. This can only happen if the migration of the cells is slow and the tendency to return to the original type is strong.

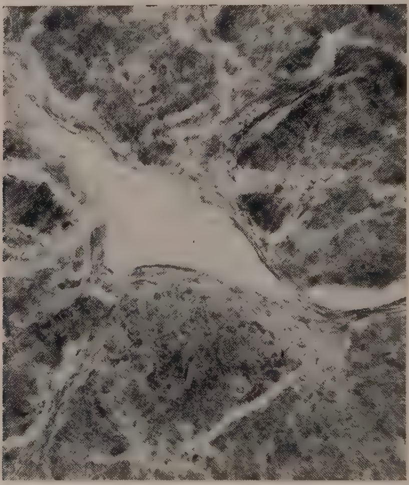

FIG. 42 (Case A80564).—Metastasis in anorectal lymphnode. Cells show first degree of cytodifferentiation. (× 100.)

Group 3.—There were seventeen patients (17 per cent) in this group. Ten were males and seven were females. This is about the average for the entire series, so that sex apparently does not play a part in determining malignancy. The average age was fifty-one and two-tenths years and this also seems to show that the age does not determine malignancy to any great extent. It is true in carcinoma of the rectum as in all carcinomas in the body that the most malignant types of growth occur in very young persons. The average duration of symptoms was seven and four-tenths months which is almost four months less than the average for the other groups. While this group is too small for definite conclusions to be drawn, it would seem to show that in the more rapidly growing types the symptoms are such as to cause patients to seek medical advice earlier. The average number of glands for each specimen was six and one-tenth. Table 4 gives the sex, age, duration of symptoms, total number of glands found, and total number of glands involved for each specimen in the group.

TABLE 4

GROUP 3. CASES OF CARCINOMA OF THE RECTUM WITH METASTATIC INVOLVEMENT OF ONE-HALF OR MORE THAN ONE-HALF OF THE LYMPH NODES

Case.	Sex.	Age.	Duration of symptoms, months.	Glands dissected out.	Glands involved.
928M	F.	69	3	2	2
4831½J	M.	50	6	5	4
A7039	F.	65	24	7	7
A7624	F.	64	8	5	3
A7631	F.	60	12	5	3
A21961	M.	33	4	5	5
A23639	M.	54	5	6	3
A52248	M.	54	3	6	3
A74532	F.	43	36	12	6
A78911	M.	39	3	8	7
A85834	M.	56	4	4	2
A108406	M.	55	7	5	3
A110220	M.	64	1.5	3	2
A121346	F.	29	6	6	3
A139873	M.	60	2.5	6	3
A168690	M.	40	1.5	11	10
A217336	F.	36	1.7	9	9

The characteristic type of growth in Group 3 is seen to be the ulcerative (Figs. 43 and 44) and most of the growths were much smaller than the average of Group 1. The specimens (Fig. 44) resembled the growths in Group 2 in breaking through the muscular coats of the bowel, but their dissemination into the fatty tissue surrounding the bowel was

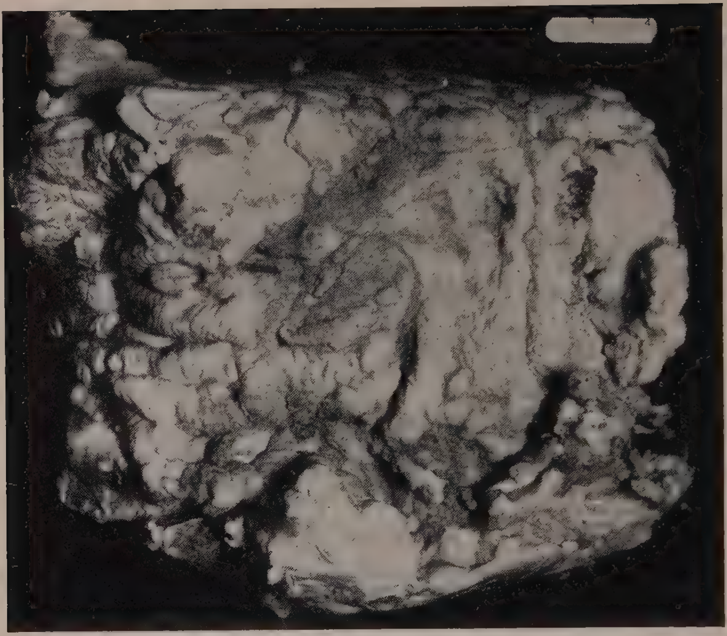

Fig. 43 (Case A121346).—Typical specimen of Group 3.

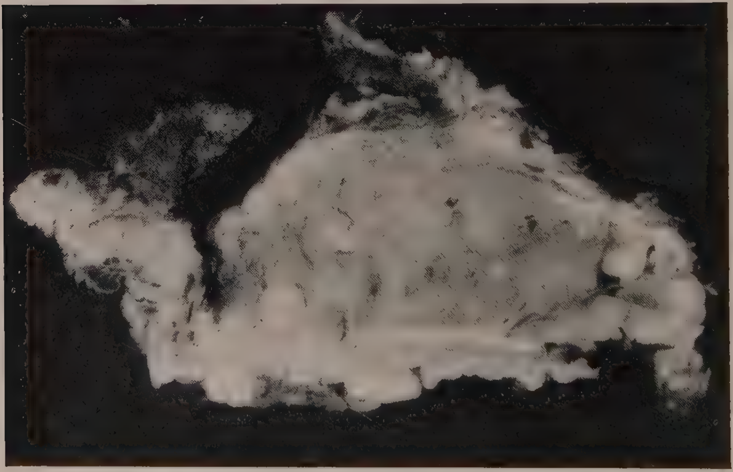

Fig. 44.—Longitudinal section of growth shown in Fig. 43.

much less. Metastasis occurs early to the nodes (Figs. 45 and 46) before direct extension far into the surrounding tissues has taken place.

Early glandular involvement affects so small a part of the gland that it can only be ascertained by microscopic examination. The lymph sinuses at the edge of the gland are first affected (Fig. 47).

Smith says, "There is need for further investigation on this subject (speaking of glandular involvement in carcinoma of the rectum), but I think sections of all glands from a series of rectal growths would prove that glandular invasion is not wide-spread in the stages early enough to be operable." This statement based on clinical experience is partially borne out by this study. Fifty-three per cent of the patients did not have involvement of the glands, 30 per cent had partial involvement, and 17 per cent had marked involvement. Oehler reports that 38 per cent of the fifty-four patients who died from carcinoma of the rectum and on whom necropsies were performed had glandular involvement in

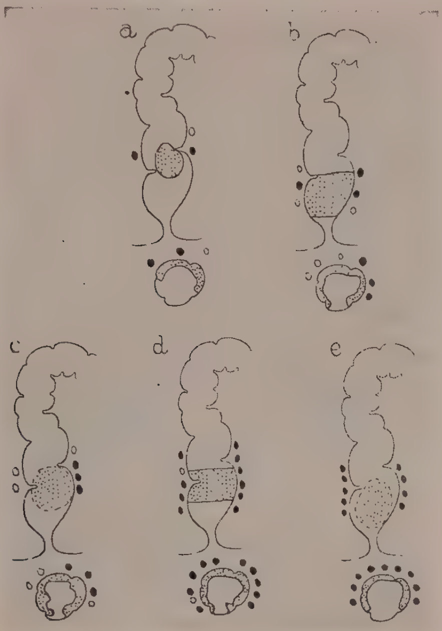

FIG. 45.—Diagram showing relative position of glands and growth in five cases of Group 3. Glands not involved are shown as clear circles; glands involved are shown in solid black. a (Case A110220). Encircling growth measuring 40 by 30 mm.; 9 cm. from anus. b (Case A121346). Encircling growth measuring 70 by 50 mm.; 5 cm. from anus. c (Case A139873). Growth on anterior wall measuring 80 by 60 mm.; 7 cm. from anus. d (Case A168690). Encircling growth measuring 55 by 60 mm.; 7 cm. from anus. e (Case A217336). Growth on anterior wall measuring 35 by 40 mm.; 3 cm. from anus.

the retroperitoneal lymph nodes. In Pennington's collected cases, 32 per cent showed some involvement of the regional lymph nodes. In neither instance was it stated that all the nodes were systematically examined. MacCarty and Blackford found 52 per cent of 200 patients with carcinoma of the stomach to have glandular involvement. The close agreement of their percentages for the stomach and of these presented in this paper for the rectum is striking. It may mean that about one-half of the growths of the gastro-intestinal tract give rise to metastatic glandular involvement.

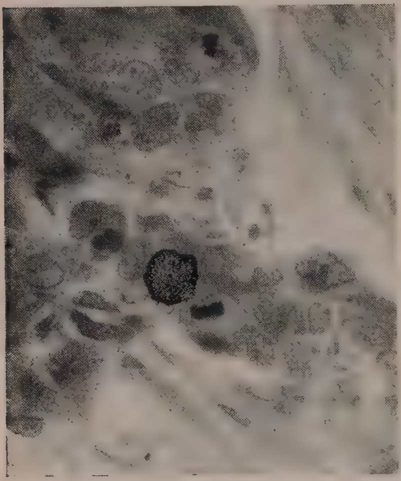

FIG. 46 (Case A85834).—Metastasis in lymph-node. First degree of cytodifferentiation. Cells have large, clear nuclei with prominent nucleoli; two mitotic figures may be seen. (× 500.)

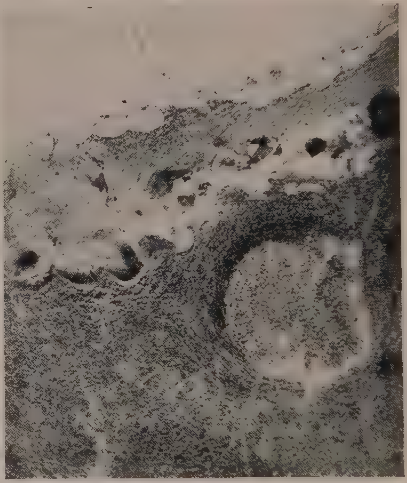

FIG. 47 (Case A110220).—Beginning involvement in peripheral lymph sinus, which could be determined by microscopic examination only. (× 50.)

A systematic examination of the glands affords a more accurate idea of the prognosis in a given case. In studying the glands in Case A80564 (Fig. 42) the following note was made: Sections show but little evidence of differentiation; the tumor should be rapidly growing. One should expect a short history and a poor result. When the history of the patient was consulted later it was found that the symptoms had been present only six weeks. Operation was performed by the Mayo-Kraske method and the growth entirely removed. The patient returned to the Clinic six months later, and it was found that the disease had metastasized to the liver. He died shortly afterwards. The question of operability is often clinical, but the question of prognosis, aside from operative prognosis, is one which can only be accurately and safely answered by the aid of the microscope.

SUMMARY

Rectal carcinomas are the most common form of intestinal neoplasms and make up 4 per cent of all the cancers of the body. The majority of patients are in the sixth decade. The males predominate slightly. The location of the growth on the rectal wall varies. About as many occupy the anterior wall as the posterior. The greater number of the growths are from the ampulla to the rectosigmoidal juncture. Adenocarcinoma is the most common type. Metastasis to the glands usually takes place slowly and the liver is the organ most affected by secondary growths. The other organs of the body are only rarely affected.

The size of the growth in the rectum cannot be relied on as an accurate index of the probable lymphatic involvement. The growths without lymphatic involvement tend to grow into the lumen of the bowel. The growths with slight lymphatic involvement tend to spread by direct extension and are slow growing. Carcinomas of the rectum with extensive lymph glandular involvement tend to metastasize through the lymph stream early. Occasionally metastasis may take place by emboli breaking off into the portal veins.

Metastatic lymph glandular involvement can only be definitely determined by systematic microscopic study of all the regional lymph nodes. The size of the lymph node is not an efficient means of determining whether or not there is metastatic involvement. This is especially true if the amount of involvement is small, or if the process is an early one.

Systematic microscopic examination of all the regional lymph nodes in carcinoma of the rectum offers as it does in cancer of the stomach the best method of establishing an accurate prognosis for the case.

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ACTINOMYCOSIS OF THE GASTRO-INTESTINAL TRACT: A STUDY OF FOURTEEN CASES*

JAMES CHESTER BROGDEN

The diagnosis of actinomycosis of the intestinal tract is rarely made until late after sinus formation and extensive involvement of the intestines, liver, or other organs has taken place, and after surgical excision of the diseased area is impossible. Therefore, any mass which occurs in the lower part of the abdomen in the region of the ileocecal juncture, particularly one associated with a persistently discharging sinus, should be regarded with suspicion. Repeated examination of the discharge, pathologic examination of tissue from the mass or from the walls of the sinus, marked loss of weight and strength, pronounced anemia, flexion of the thigh without disease of the vertebral column or hip joint, and marked constipation rarely fail to establish the correct diagnosis.

DIFFERENTIAL DIAGNOSIS

In the differentiation of tumors of the intestine and actinomycosis, carcinoma should be particularly considered. Its course is more chronic, it increases in size very slowly, anemia is not as pronounced, diarrhea with blood in the stools is more often observed, the mass is generally movable, is not tender, and shows little or no tendency to invade the abdominal wall or to form sinuses. Early diagnosis of both conditions can be made only by operation and pathologic examination of the tissue.

The differentiation of tuberculosis of the intestine and actinomycosis is also difficult until the later stages. Tuberculosis often forms a chronic, slow-growing tumor in the intestine, usually associated with pulmonary tuberculosis; diarrhea is common, but there may be constipation. Sinuses do not form; the growth is slower, the mass generally movable, and tuberculosis bacilli can sometimes be found in the stools. The adjacent organs, particularly the liver, are not affected as in actinomycosis. Tuberculosis, carcinoma, and actinomycosis of the intestines all show a filling defect on roentgen-ray examination of the colon. In all there is anemia, loss of weight and strength, and in tuberculosis and actinomycosis, elevation of temperature after secondary infection takes place.

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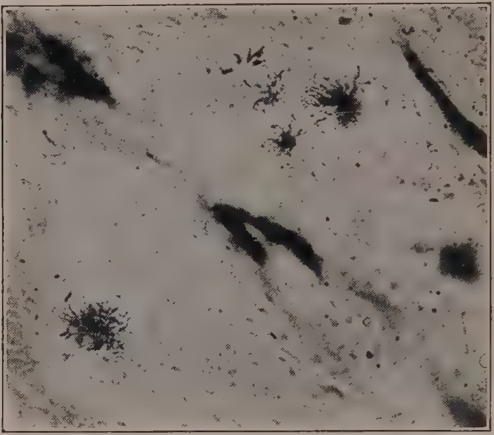

Fig. 48 (Case A210659).—*Actinomyces bovis* in the tissues. (× 200.)

Appendiceal abscess is often the beginning of actinomycosis infection, but most observers believe that the appendicitis is caused by the pyogenic bacteria and that this break in the mucosa allows the ray-fungi to penetrate the connective tissue in the wall of the intestine where

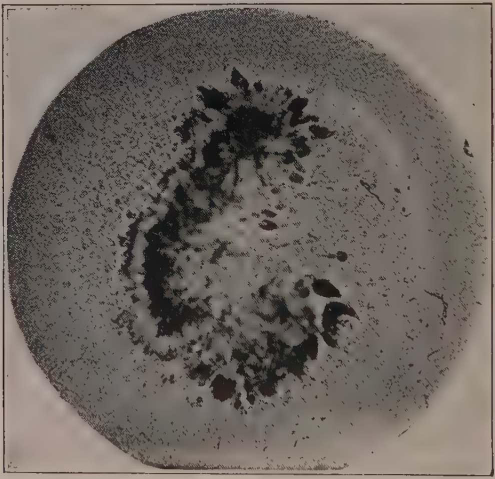

Fig. 49 (Case A210659).—*Actinomyces bovis* showing mycelia and clubs. Extensive round-cell infiltration and necrosis are around the organisms.

they begin to grow. *Actinomyces bovis* have been found in the lumen of the appendix without inflammatory changes in the mucosa. Tubal abscess and localized peritonitis are more acute; they cause marked elevation of temperature. Pain is more intense, and constitutional reaction is more or less marked.

In gumma of the liver there is a history of infection; the Wassermann reaction is generally positive and other syphilitic lesions in the body establish the differentiation. In actinomycosis the abscess of the liver is always secondary to a primary focus in the intestine, or, rarely in the thorax. In amebic abscess of the liver there is a history of diarrhea and the ameba can often be found in the stools. There is no tumor in the lower abdomen and no discharging sinus. At operation the ameba can often be found in the purulent material in the abscess, while in actinomycosis the ray-fungi are easily recognized.

PROGNOSIS

The prognosis depends on the degree, nature, and extent of the lesions, the virulence of the organism, the resistance of the individual, and the time treatment is instituted. If an early diagnosis is made so that complete resection of the intestine and the diseased area can be accomplished, and vigorous iodid, and roentgen-ray and radium treatments are given, the prognosis is fairly good. In the later stages, with involvement of the other organs in the abdomen and sinus formation, the possibility of a cure is always doubtful; most observers place the mortality from intestinal actinomycosis at 60 to 70 per cent.

In the series of fourteen patients studied in the Mayo Clinic, no report of present condition could be obtained of three; one has been treated for only four weeks. Six of the remaining ten are dead, with an average length of life after onset of the disease of three years. One patient was operated on and had no symptoms of recurrence four years afterward. One patient is apparently cured after four years of medical treatment, and two are markedly improved after taking iodids, and roentgen-ray and radium treatments.

TREATMENT

The treatment may be surgical, medical, or hygienic. Surgical treatment is usually successful only when the disease is still localized and foci of infection can be completely removed. After sinus formation and secondary involvement of adjacent structures, the sinuses should be laid open, necrotic tissue curetted out, the wound packed with iodoform gauze or swabbed with strong tincture of iodin, and later irrigated with antiseptic solution, such as 1 per cent copper sulphate or 4 per cent formalin.

The drugs generally used in the treatment are the iodids and copper sulphate. Potassium iodid is given by mouth in rapidly increasing doses of from 25 to 60 grains to 200 grains three times a day. Sodium iodid, 10 per cent solution, is given intravenously at first in doses of 20 to 30 c.c. and rapidly increasing to 100 c.c. a day. Copper sulphate, 0.5 grain three times a day, is being used by some authorities who report excellent results in both actinomycosis and blastomycosis. Yeast by mouth daily, with salvarsan 0.2 to 0.6 gm. every six to eight days, has been tried, but without noticeable good results. Roentgen ray and radium, continued over a long period combined with the iodids, are giving the best results and are generally successful in the early stages of the disease. Tonics and stomachics are given.

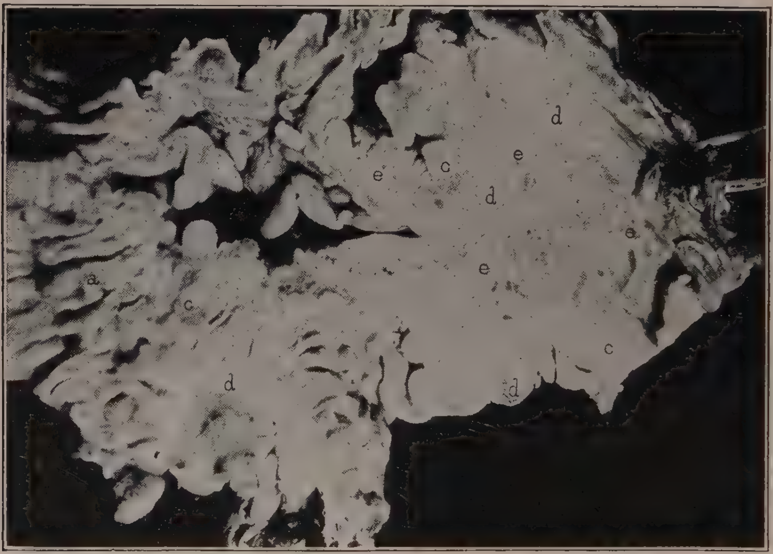

Fig. 50 (Case A210659).—Section of resected mass showing (a) cecum, (d) areas of marked fibrous tissue formation, and (e) areas of central necrosis.

Fresh air, sunshine, moderate exercise, an easily digested, nourishing diet, or even forced feeding, are absolutely essential, especially in the later stages in which cachexia, and loss of weight and strength are marked.

However, a review of the literature[1-13] on the subject and study of this series show that prognosis is unfavorable in all cases of actinomycosis of the intestinal tract. The mortality is 60 to 70 per cent. Treatment is successful only when diagnosis is early, before sinus formation and involvement of adjacent organs, so that the primary foci can be entirely removed and later roentgen-ray, radium, and the iodid treatments given. A study of fourteen cases of actinomycosis of the gastro-intestinal tract in the Mayo Clinic since 1909 seems to warrant conclusions as follows:

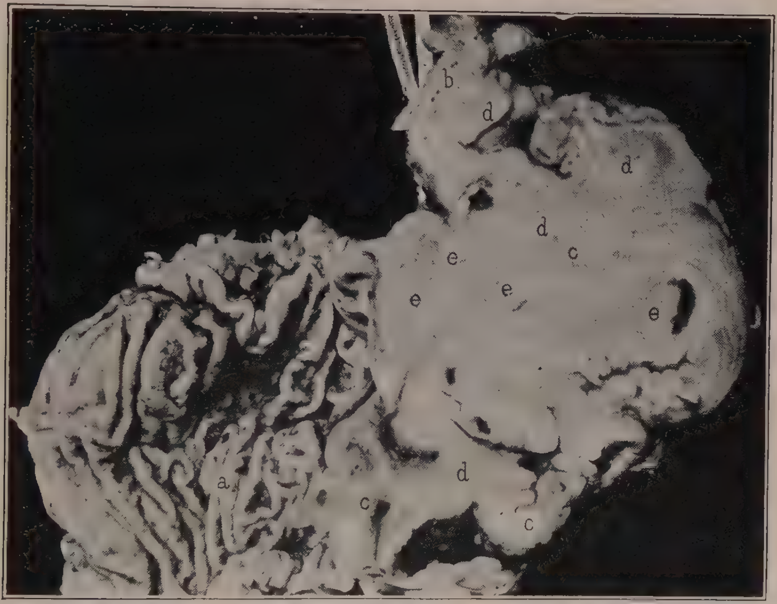

Fig. 51 (Case A278991).—Section of resected mass showing (a) cecum, (b) ileum, (d) dense fibrous tissue, and (e) areas of necrosis.

1. Actinomycosis of the gastro-intestinal tract is not so rare as has been generally believed; thirteen of the fourteen Mayo Clinic cases occurred in the last four years.

2. The acute form is more common; it usually begins as a typical attack of acute appendicitis. There may be one severe or several mild attacks. Six of the patients in the series gave histories of operation when a ruptured, gangrenous appendix had been removed immediately preceding the appearance of the mass. The chronic form is insidious in onset with very slight indefinite pain in the lower abdomen.

TABLE 1.—TABULATION OF CASES

Case, date.	Sex, age.	Occupation, location.	Symptoms and previous treatment.	Findings at examination.	Diagnosis.	Treatment.	Remarks.
A30603 10/18/09	M. 51	Druggist, Iowa.	For five years attacks of dull pain in right side of abdomen lasting one to three days. July, 1908, severe pain for twelve hours and mass in upper abdomen, pain and tenderness increasing.	Tender mass in right upper quadrant of abdomen, increased liver dullness.	Intestinal actinomycosis with sinus formation, actinomycetes found in pus in January, 1916.	At operation, October 30, 1909, abscess in gallbladder region drained, 180 c.c. pus and much necrotic tissue. Second operation, December 12, 1909, pelvic abscess drained through right lower quadrant. Potassium iodid by mouth. January, 1916, another abscess drained in left lower quadrant.	Patient died February, 1917, from extension to liver and thorax.
A148995 12/31/15	M. 40	Plumber, Ohio.	March, 1916, dull pain in left lower quadrant lasting five days; similar attack in July lasted three weeks. October 6 severe pain in right lower quadrant made operation necessary.	Large, hard, indurated mass in right lower quadrant with two sinuses discharging yellowish pus. Hemoglobin 41 per cent, leukocytes 13,000.	Intestinal actinomycosis with sinus formation, pus showed actinomycetes.	Sodium iodid intravenously and potassium iodid by mouth.	In 1917 the patient reported that no mass could be felt; he had gained in weight.
A207771 7/12/17	M. 35	Farm laborer, often worked with cattle with lumpy jaw. Montana.	For fifteen years recurrent attacks of dull pain in right lower quadrant. Since appendectomy, June, 1917, sinus in old wound drained yellowish pus.	Sinus draining yellow pus and hard, irregular mass in right lower quadrant.	Intestinal actinomycosis involving abdominal wall with sinus formation, actinomycetes from tissue from abdominal wall and pus.	Massive doses of potassium iodid by mouth and roentgen ray.	Patient died in 1919, cause unknown.
A207688 9/11/17	M. 33	Farmer, Saskatchewan	Pain in lower abdomen since removal of ruptured gangrenous appendix in September, 1916. At laparotomy in November many adhesions and much scar tissue at site of previous operation was found. A persistently draining sinus made another operation necessary in March, 1917. Pain became more severe and in June abscess drained over right sacral region, and in August abscess over left sacral region.	Distended abdomen, slight tenderness and induration of right lower abdominal wall with two sinuses to right and left of middle of sacrum discharging yellowish pus. Hemoglobin 40 per cent, leukocytes 4,800.	Abdominal actinomycosis with retroperitoneal abscess.	Four transfusions. Sodium iodid intravenously daily; 50 c.c. 10 per cent solution at first, gradually increased to 200 c.c., and tonics.	Patient continued treatment at home. No later report received.

TABULATION OF CASES—*Continued*

A210659 10/12/17	F. 53	Housewife, husband a furniture dealer. Iowa.	In 1915 dull pain in right upper quadrant radiating to back, with nausea and vomiting of bile. In June acute generalized abdominal pain localizing in right lower quadrant, associated with slightly increased temperature, nausea, and constipation. Mass in right lower quadrant one month later.	Large, irregular, slightly movable, and slightly tender mass in right lower quadrant. Hemoglobin 58 per cent, leukocytes 12,000, roentgenogram of colon revealed filling defect in ileum and cecum.	Actinomycosis of ileum, cecum, appendix, and colon, actinomycetes in tissue (Figs. 1 and 2).	At operation, October 17, 1917, ileocecal coil, appendix, part of hepatic flexure, and 10 cm. ileum removed (Fig. 3). Radium and roentgen ray, sodium iodid intravenously, and potassium iodid by mouth.	In 1919, patient reported condition good, no symptom of recurrence in abdomen.
A211906 10/25/17	F. 30	Housewife, husband electrical engineer. Iowa.	November, 1916, dull pain on both sides of lower abdomen with slightly increased temperature and metrorrhagia. At operation elsewhere in December for suspected ectopic pregnancy ovaries, tubes, and appendix found in suppurating mass. They were removed. Discharging sinus remained. July, 1917, large mass of cartilaginous consistency removed from pelvis.	Slightly tender mass in hepatic region, large, hard mass in pelvis. Slightly increased temperature and emaciation, hemoglobin 20 per cent, leukocytes 14,000.	Intestinal actinomycosis with extension to pelvis and liver.	Four transfusions between December 4, 1917 and January 3, 1918. April 9, abscess below right breast drained. Frequent roentgen ray, large doses of potassium iodid by mouth, sodium iodid intravenously, tincture of digitalis, and Blaud's pills.	Patient dismissed after six months to continue treatment at home. Death in 1919, exact cause unknown.
A224617 3/11/18	M. 26	Farmer, Saskatchewan.	In February, 1917, abdominal distention with chills, fever, and sweats. In April abscess in left upper abdomen discharged green pus. In May and July two more abscesses with persisting, discharging sinuses. Marked loss of weight.	Fluid in left chest and four discharging sinuses in lower and upper left quadrants of abdomen. Temperature 101, pulse 124, hemoglobin 50 per cent, leukocytes 15,000.	Intestinal actinomycosis with secondary involvement of thorax.	Four aspirations of chest. Massive doses potassium iodid for one month. Treatment carried on at home.	Patient died in 1920.
A235668 6/19/18	F. 43	Housewife, husband farmer, North Dakota.	Dull pain in lower abdomen and mass in right lower quadrant for three months, with dysmenorrhea and marked constipation.	Mass palpable below the umbilicus, skin over mass bluish red and indurated. Slight anemia.	Intestinal actinomycosis with involvement of abdominal wall.	Roentgen ray and potassium iodid by mouth.	Several abscesses on abdominal wall ruptured, patient gained in weight, mass not increased in size.

TABULATION OF CASES—*Continued*

Case, date.	Sex, age.	Occupation, location.	Symptoms and previous treatment.	Findings at examination.	Diagnosis.	Treatment.	Remarks.
A278991 7/15/19	M. 42	Farmer, Saskatchewan.	Soreness and dull pain across lower abdomen lasting one to three days, marked constipation. In June, 1919, severe attack of pain made operation necessary. Mass at ileocecal coil and many adhesions found, appendix removed.	Slightly tender, hard mass 8 cm. in diameter in right lower quadrant. Roentgenogram revealed filling defect of ileocecal juncture.	Malignancy of cecum.	At operation, July 25, 1919, large mass found involving ileocecal coil and adjacent parts of ileum, cecum, and ascending and transverse colon, 22.5 cm. resected (Fig. 4). Six arsphenamin injections and massive doses of potassium iodid by mouth.	Patient died February 19, 1920. Partial necropsy by home physician showed slight recurrence at site of operation.
A325922 7/21/20	M. 39	Farmer, Saskatchewan.	From 1913 to 1920 seven attacks of severe pain in right lower quadrant lasting three to six days. At operation during last attack ruptured gangrenous appendix and 10 cm. gangrenous bowel removed. Sinus drained since. Marked constipation and loss of 20 pounds.	Hard, indurated mass in right lower quadrant and three draining sinuses. Hemoglobin 50 per cent, leukocytes 13,800.	Intestinal actinomycosis with sinus formation, actinomycetes in pus from sinuses.	Roentgen ray and massive doses of potassium iodid by mouth.	Patient died January, 1921, from cachexia and extension to thorax.
A332130 8/31/20	M. 36	Farmer, Iowa.	August, 1919, small lump in right lower abdomen; in March, 1920, it extended to umbilicus. Pathologic diagnosis from piece of excised tissue was chronic inflammatory tissue. Small abscess opened and drained, discharging sinus remained. Two attacks of diarrhea, usually constipation. Eleven injections of autogenous vaccine given without benefit.	Large, hard, irregular mass in right lower quadrant with draining sinus, skin bluish red and indurated. Roentgenogram revealed filling defect in cecum and ascending colon. Hemoglobin 55 per cent, leukocytes 9,800.	Actinomycosis of cecum and ileum involving abdominal wall.	Roentgen ray, massive doses of potassium iodid, and tonics.	Patient not traced.
A336397 10/5/20	M. 27	Tile mill owner, Indiana.	May, 1920, loss of weight and strength associated with malaise and cough. In June attack of pain in right lower quadrant with vomiting lasting one week, small lump in right lumbar region was opened and drained, right thigh partially flexed on abdomen.	Large, irregular, hard mass in right lower quadrant with discharging sinus in right lumbar region. Leukocytes 12,000.	Intestinal actinomycosis with sinus formation, pus from sinus showed actinomycetes.	Roentgen ray and massive doses of potassium iodid by mouth.	Patient not traced.

TABULATION OF CASES—*Concluded*

A341474 11/20/20	M. 30	Telegraph operator, Montana.	In 1913 attacks of dull pain across lower abdomen radiating to thigh and right hip, difficulty in extending right thigh. In 1917 severe attack in right lower abdomen, pain radiating to costal margin and right lumbar region. Unsuccessful exploration of gallbladder and right kidney elsewhere followed by profuse discharge of pus for seven weeks; mild attacks of pain continued. Operation elsewhere disclosed gangrenous appendix and abscess of abdominal wall; sinus remained.	Four discharging sinuses and hard, tender mass in right lower quadrant, skin over mass bluish red and indurated.	Actinomycosis of cecum and abdominal wall, actinomycetes found in pus from sinuses.	Roentgen ray, radium, and large doses of potassium iodid by mouth. Treatment continued by home physician.	Condition much improved after two months.
A351274 3/1/21	F. 23	Housewife, husband general merchant, North Dakota.	December, 1918, general abdominal pain localizing in right lower quadrant. Pelvic abscess drained through vagina for three weeks. At exploratory laparotomy elsewhere appendix, both tubes, and one ovary found in mass of adhesions and removed. January, 1920, recurrence of pain and hard, tender mass in right lower quadrant, second laparotomy. Since then dull pain in abdomen radiating down right hip and side; sinus at old incision drained since June, 1920.	Hard, nodular mass in right iliac fossa and pelvis not connected with uterus; two draining sinuses in lower abdomen; skin bluish red and indurated around sinuses. Moderate anemia, leukocytes 15,300.	Intestinal actinomycosis with extension to pelvis and abdominal wall.	Roentgen ray, potassium iodid by mouth, and sodium iodid intravenously.	Patient still under treatment.

There may be practically no pain, the mass being the first sign of the disease.

3. In both forms marked loss of weight and strength, pronounced anemia, induration and a bluish red discoloration of the skin over the mass and around the sinuses, and pain down the right thigh with flexion of the thigh on the abdomen are characteristic symptoms. Diarrhea is not a constant symptom of the disease. Constipation was the rule in the fourteen cases.

4. The anaërobic organism, *Actinomyces bovis*, which possibly normally inhabits the gastro-intestinal tract, is the cause of the disease. The ileocecal coil is most often affected; the stomach and upper small intestine are practically immune.

5. Carious teeth, diseased tonsils, bad hygienic surroundings, over crowding, or anything to lessen body resistance are predisposing factors. It is doubtful if the disease is transmitted from cattle to man. In three of the fourteen cases there was a definite history of exposure to lumpy jaw in cattle.

6. A chronic discharging sinus in the lower abdomen, especially after operation and drainage of an appendiceal abscess, should arouse suspicion of actinomycosis, and repeated examinations for the ray-fungi should be made. A few cases are not diagnosed because the yellow granules are not found at the first examination. Repeated examinations of the purulent material over long periods, with pathologic examination of the tissue from the mass or from the walls of the sinuses, must be made before actinomycosis is ruled out.

7. Early operation and excision of the diseased area before the infection spreads to the surrounding tissues, frequent roentgen-ray and radium treatments over the abdomen, and large doses of potassium iodid by mouth and sodium iodid intravenously offer the best hope of cure. In the later stages, after extension of the disease to the adjacent organs and sinus formation, radical surgical measures are of no avail. Some patients apparently are cured under treatment with radium, roentgen ray, and the iodids; others improve wonderfully, only to have recurrence in from two to four years.

8. Death usually occurs from cachexia and extension of the disease to the liver and thorax. The average mortality is 60 to 70 per cent.

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PRIMARY RETROPERITONEAL SARCOMA: REPORT OF TWENTY-EIGHT CASES*

CLAYTON F. ANDREWS

The term "retroperitoneal sarcoma", originated by Lobstein, usually includes both primary and secondary growths behind the peritoneum. The secondary sarcomas usually originate in the testicle or ovary and are not included in the report of cases of true primary retroperitoneal sarcoma. Growth in the latter type originates behind the peritoneum in the postperitoneal areolar tissue, adipose tissue, or lymph glands, and occasionally in the vertebrae, independently of any organ, such as the kidney or adrenal.

Steele, in 1900, reviewed the literature and reported ninety-six cases of primary retroperitoneal sarcoma, including five of his own. Trout and Meekins, in 1920, reported twelve additional cases, including two of their own, and in 1922 I collected six cases from the literature and added twenty-eight proved cases from the Mayo Clinic; a total of 142 cases. Ten cases, clinically diagnosed primary retroperitoneal sarcomas, are not included in the series since the diagnosis was not proved microscopically. No satisfactory explanation has been made with regard to the cause of these tumors. The largest tumor on record was reported by Bull and weighed 34 pounds after removal. The microscopic diagnosis of this tumor was myxofibrochondrosarcoma. This study is based on twenty-eight proved cases of retroperitoneal sarcoma at the Mayo Clinic.

The ages of the twenty-eight patients in the series ranged from two and one-half years to sixty-two years. Twenty-three of the patients were males and five were females. Rarely is more than one tumor found; multiple growths were present in one case of the series (3.5 per cent). Thirteen of the growths (46.4 per cent) were on the left side, nine (32.1 per cent) on the right, three (10.5 per cent) in the pelvis, and two (7 per cent) central; one (3.5 per cent) occupied both sides of the abdomen.

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SYMPTOMS

The symptoms are insidious, indefinite, and varied. The patients observed in the Mayo Clinic had had symptoms for from two weeks to three years, on an average for eight months. The onset is usually insidious with indefinite abdominal pain, at times colicky, nausea, vomiting, and gaseous distention. Pain in the lumbar region and in the leg is a common complaint. The attacks may simulate that due to gallstones although the pain is less severe and more constant. Steele considers diarrhea to be an important symptom; Keen's patients suffered mostly from constipation. Fourteen (50 per cent) of the patients in the Mayo Clinic series had normal bowel function, two (7 per cent) had diarrhea, eight (28 per cent) had constipation, and one had both diarrhea and constipation. Two patients had edema; as a rule it begins at the ankle and extends upward. Six (21 per cent) complained of urinary frequency, one had dysuria and hematuria, and one had ascites. Jaundice, which occurs when the common duct is pressed on by the tumor, was not present. Loss of weight is often marked and rapid and usually accompanied by great loss of strength. Nearly one-half the patients had fever, ranging from 99 to 102, during some stage of the disease. Blood counts were available in twenty-four cases; in eleven (45 per cent) hemoglobin was below 70 per cent.

The roentgen ray aided greatly the diagnosis by ruling out gastro-intestinal tumors. Its use in conjunction with the cystoscope ruled out genito-urinary masses.

The mass, usually deeply placed, may be mobile or immobile, firm or cystic, smooth or irregular, tender to touch or painless. One of the most characteristic findings is the location of the colon resting in a groove on the anterior surface of the tumor. If the mass is laterally placed, it may be impossible to distinguish it from liver, kidney, adrenal, or spleen. If it is low in the pelvis, rectal or vaginal examination may afford the most valuable information. Unusual retroperitoneal serous cysts may confuse the diagnostician, but these grow slowly and become very large. Aneurysm should readily be distinguished by the pulsation, thrill, or bruit, lack of emaciation and anemia, and slower growth. Lipomas or myxolipomas grow much more slowly and larger, show marked fluctuation, and cause pressure symptoms much later. Rapid growth in a retroperitoneal lipoma is very apt to mean sarcomatous change. The term degeneration is purposely avoided in this connection, as it has been shown that the change from benign to malignant is not one of degeneration, but of very active, though abnormal, generation. Enlarged tuberculous lymph nodes may be distinguished by the history, uniform enlargement of the abdomen, greater emaciation, shorter course, greater tenderness, higher fever, and often by the discovery of tuberculosis elsewhere in the body. It is far more common than is retroperitoneal sarcoma. The most common conditions simulating the growth are ovarian cysts and renal tumors; these can usually be eliminated by careful physical and special examinations.

Metastasis had occurred in about 33 per cent of the series; Steele found practically the same proportion. Metastasis to the liver, lungs, or lymph glands was most common, but the spleen, kidney, skin, omentum, muscle, pleura, heart, bone, spinal cord, dura, adrenal, and mesentery may show secondary nodules.

TYPE OF TUMOR

The most common type of sarcoma in the series was the small round-cell, or lymphosarcoma (Fig. 52) which occurred in ten of the twenty-eight cases. The next most common was the spindle-cell (Fig. 53) and fibrosarcoma (Fig. 54), each being present in four cases. The mixed cell, fibromyxoma, and myxosarcoma (Figs. 55 and 56) were found in two cases each. Small and medium round-cell (Fig. 57), myxo-osteochondrosarcoma (Figs. 58 and 59), and giant-cell sarcoma (Fig. 60) were found in one each; the latter was made up, for the most part, of tumor giant cells.

In the beginning the mass is usually firm and lobulated. Later, it undergoes hemorrhagic mucoid, or purulent degeneration, with the formation of a cyst. On removal, the irregular mass often is found to be encapsulated and quite hard; it may contain lobulated cysts. It offers considerable resistance to cutting. Hemorrhagic areas are not uncommon and dense whorls of fibrous connective tissue are seen. If it contains muscle it is often salmon colored; cartilage and bone appear the same here as elsewhere.

Microscopically, the cells are usually arranged in masses which extend irregularly into strands of more or less dense fibrous tissue. The sarcoma cells are usually associated with abundant capillaries composed of a single layer of endothelial cells. In some instances the blood channels have no endothelium, the blood lying in immediate apposition to the tumor cells. This probably explains the common finding of hemorrhagic degeneration and metastasis to the lungs and liver by way of the blood stream. The more highly differentiated the cells composing

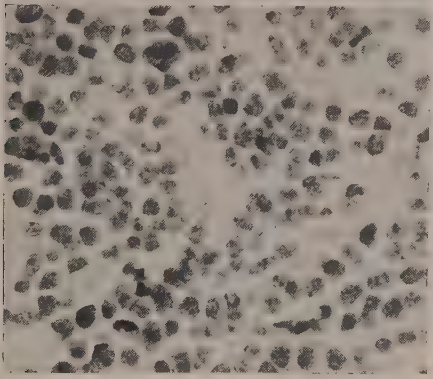

Fig. 52.—Lymphosarcoma. (× 500.)

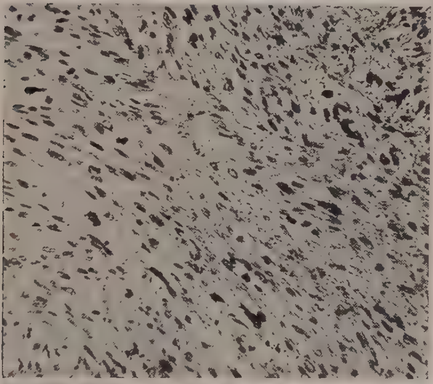

Fig. 53.—Spindle-cell sarcoma. (× 100.)

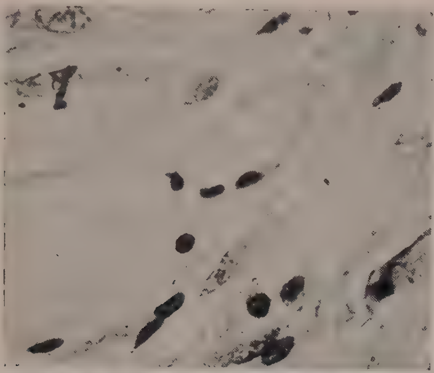

Fig. 54.—Fibrosarcoma. (× 500.)

the tumor, the more benign the neoplasm. The most malignant and infiltrative of retroperitoneal sarcomas is the lymphosarcoma, which is the least differentiated. The cells are massed closely, have single deep-staining nucleoli, and contain little cytoplasm; there is very little interstitial connective tissue. In the rapidly growing types, unfortunately the most common types, mitotic figures may be seen.

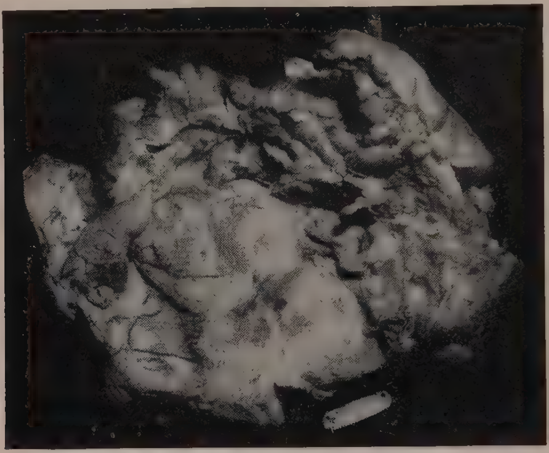

FIG. 55.—Myxosarcoma, 3,900 gm.

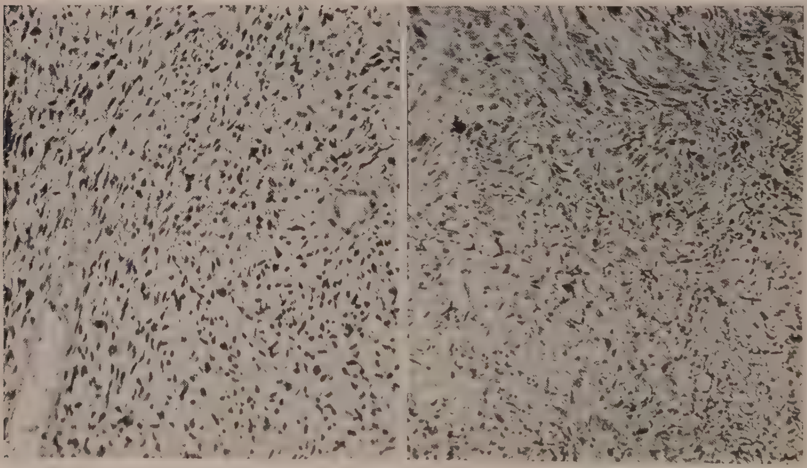

FIG. 56. FIG. 57.

FIG. 56.—Myxosarcoma. (× 100.)

FIG. 57.—Mixed round-cell and spindle-cell sarcoma. (× 100.)

The medium and large round-cell sarcoma are much less common and also less malignant than the small round-cell type. The cells may be round or oval, the cytoplasm abundant, and the nuclei large. There is more likely to be connective tissue between the cells. Such neoplasms are less destructive and break down more slowly than do the lymphosarcomas.

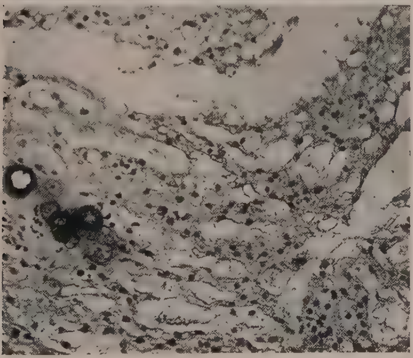

Fig. 58.

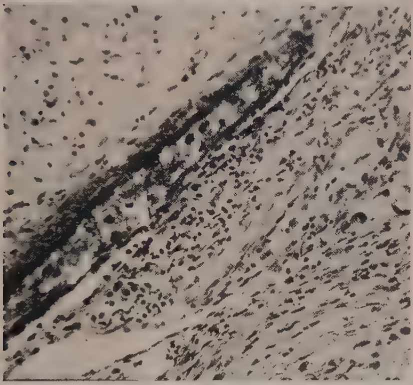

Fig. 59.

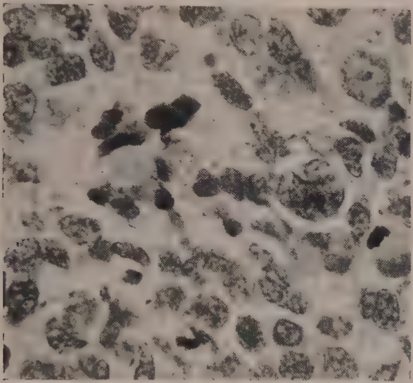

Fig. 60.

Fig. 58.—Myxo-osteochondrosarcoma; stellate cells and area of cartilage. (× 100.)
Fig. 59.—Same as Figure 58. Area of bone formation. (× 100.)
Fig. 60.—Giant-cell sarcoma. (× 500.)

Summary of Cases

Case, date.	Sex, age.	Duration of symptoms.	Date of operation.	Findings at operation.	Pathologic diagnosis.	After course.
A36910 4/26/10	M. 40	Three weeks.	4/27/10	Retroperitoneal sarcoma, 12 by 12 by 18 cm., originating in inner layer of mesosigmoid.	Fibrosarcoma.	Death from recurrence October, 1911.
A37608 5/14/10	M. 31	Five months.	5/21/10	Inoperable, retroperitoneal sarcoma involving lymph nodes.	Lymphosarcoma.	Death October, 1910.
A69466 6/20/12	F. 6	Six months.	....	....	Giant-cell sarcoma (Fig. 9).	Unknown.
A71100 7/25/12	M. 54	Uncertain.	8/2/12	Inoperable, retroperitoneal sarcoma at head of pancreas under middle part of duodenum and near hepatic flexure; adherent to liver.	Oval and spindle-cell sarcoma.	Death February 22, 1914.
A99151 1/19/14	M. 19	Four months.	1/21/14	Inoperable retroperitoneal tumor in left iliac fossa with erosion of inner surface of ilium.	Lymphosarcoma.	Death May 19, 1914.
A101025 2/21/14	M. 29	Three months.	2/25/14	Retroperitoneal sarcoma, 2 by 4 by 9 cm., in region of tail of pancreas.	Small and medium round-cell sarcoma.	Metastatic nodule behind ear; death from recurrence April 19, 1914.
A129170 4/20/15	M. 4	Ten months.	4/23/15	Inoperable retroperitoneal sarcoma, 15 by 7.5 cm., with metastasis to glands along aorta.	Lymphosarcoma (Fig. 1).	Death August 6, 1915.
A130262 5/6/15	M. 32	Two weeks.	11/12/15	Inoperable sarcoma in lower part of abdomen pushing mesentery of small intestine forward.	Small spindle-cell sarcoma.	Unknown.
A157750 4/23/17	M. 43	One year.	5/4/17	Inoperable retroperitoneal sarcoma in region of right flank.	Fibromyxosarcoma.	Unknown.

A174094 10/2/16	M. 57	One year.	10/6/16	Inoperable tumor filling pelvis and lifting bladder into abdomen and crowding sigmoid behind it.	Spindle-cell myxosarcoma.	Unknown.
A174518 10/5/16	M. 45	Two years.	10/17/16	Inoperable retroperitoneal sarcoma extending from diaphragm almost to pelvis brim, displacing large vessels to right, adherent to spleen.	Lymphosarcoma.	Death November, 1916.
A187820 5/9/17	M. 31	Three years.	3/24/17	Tumor 20 cm. in diameter growing from sacrum, internal surface of ilium, and lower lumbar vertebræ with metastasis to both lungs.	Fibrosarcoma.	Death March 25, 1917.
A194292	M. 48	Ten months.	5/21/17	Inoperable retroperitoneal sarcoma with metastatic nodules in the liver.	Mixed round-cell and spindle-cell sarcoma (Fig. 6).	Death November, 1917.
A197918 6/15/17	M. 62	One year.	6/25/17	Inoperable retroperitoneal sarcoma, 20 cm. in diameter, originating in right iliac fossa and extending upwards, dense adhesions to peritoneum.	Mixed-cell sarcoma.	Death December 25, 1917.
A201215 7/17/17	F. 59	Five months.	7/24/17	Inoperable retroperitoneal sarcoma attached to bladder and several loops of small intestine and colon.	Spindle-cell sarcoma (Fig. 2).	Death December 16, 1917.
A227733 4/12/18	F. 32	Four and one-half weeks.	4/25/18	Inoperable retroperitoneal sarcoma behind stomach and colon.	Lymphosarcoma.	Death September 2, 1918.
A229340 4/27/18	M. 61	Four weeks.	5/4/18	Degenerating retroperitoneal lipoma attached to lower pole of right kidney, weighing 3,900 gm., occupying entire right side, and extending to brim of pelvis on left (Fig. 4).	Myxosarcoma (Fig. 5).	Unknown.

SUMMARY OF CASES—*Continued*

Case, date.	Sex, age.	Duration of symptoms.	Date of operation.	Findings at operation.	Pathologic diagnosis.	After course.
A230176 5/2/18	M. 57	One year.	5/3/18	Inoperable retroperitoneal tumor, 30 cm. in diameter, with broad attachments to all surrounding tissues.	Lymphosarcoma.	Tumor greatly enlarged; patient has lost greatly in weight and strength.
A246653 9/24/18	M. 44	Three and one-half weeks.	10/2/18	Inoperable retroperitoneal sarcoma behind cecum and mesentery of small intestine.	Lymphosarcoma.	Patient received roentgen ray for several weeks. In February, 1919, had gained 4 pounds; was without pain and was working.
A250614 11/11/18	M. 32	One year.	11/14/18	Retroperitoneal sarcoma attached to right kidney extending from diaphragm to brim of pelvis.	Fibrosarcoma.	Patient received roentgen ray, radium, and Coley's serum; January 10, 1919, he had gained 75 pounds and was in good general condition.
....	....	....	6/13/20	Recurrent retroperitoneal sarcoma, weighing 350 gm., with metastatic nodules in liver and retroperitoneal tissue below the diaphragm.	Fibrosarcoma (Fig. 3).	Death, time uncertain.
A251374 11/21/18	M. 42	One year.	12/3/18	Inoperable retroperitoneal sarcoma filling entire right side and extending across median line.	Spindle-cell sarcoma.	Death a few months later.
A275504 6/16/19	F. 2.5	Eleven months.	6/24/19	Inoperable tumor situated retroperitoneally filling entire abdomen.	Fibrosarcoma.	Death November 13, 1920.
A291541 8/1/19	M. 48	One and one-half months.	10/13/19	Two retroperitoneal tumors on left side; one 30 by 15 cm.	Myxofibrolipoma.	Patient returned to Clinic August 9, 1921, with palpable mass in abdomen.

....	....	Six weeks.	8/15/21	Recurrent retroperitoneal tumor 20 cm. in diameter below pole of left kidney.	Myxofibrosarcoma.	Unknown.
A295043 10/30/19	M. 41	Ten months.	11/5/19	Tumor, 12 cm. in diameter, filled with gelatinous bloody material. The sacrum was honeycombed.	Myxochondrosteosarcoma (Figs. 7 and 8).	Recurrence July, 1920.
A297816 11/24/19	M. 3	Six weeks.	12/5/19	A hard tumor, 8 cm. in diameter, behind the bladder in the region of the prostate.	Myxosarcoma.	Death from recurrence March 18, 1920.
A304223 1/26/20	M. 26	Three months.	1/31/20	Inoperable tumor almost filling the pelvis adherent to loops of intestine; involvement of inguinal glands.	Lymphosarcoma.	Patient in good general condition.
A319811 6/14/20	F. 39	Four months.	6/23/20	Inoperable apparently retroperitoneal tumor behind unbilicus with metastasis to the inguinal glands.	Lymphosarcoma.	November 30, 1920, patient was in good general condition.
A342361 11/30/20	M. 42	Five months.	....	....	Lymphosarcoma.	January 4, 1921, death from bronchopneumonia. Necropsy revealed a retroperitoneal lymphosarcoma with metastasis to the great omentum and mesenteric lymph nodes.

Large and small spindle-cell sarcomas show the typical elongated, somewhat pointed cells with oval or spindle-shaped nuclei. These cells are arranged in bundles around the capillaries, with quite definite interstitial connective tissue. They are far less malignant than the round-cell sarcomas. It is not uncommon to find a mixture of all these types as is illustrated in Case 13 of the series. Also the tumors may be combined with various other tissues to form the so-called intermediate types, as illustrated by the osteosarcomas, chondrosarcomas, liposarcomas, myxosarcomas, fibrosarcomas, and so forth. True bone, cartilage, fat, muscle, or fibrous tissue is found in these tumors, with masses of closely packed, rapidly growing, malignant cells.

Giant-cell sarcomas make up only a small part of retroperitoneal tumors. The one giant-cell sarcoma in our series originated, apparently, from the vertebrae, near the bifurcation of the aorta. Giant cells may be present in many sarcomas, but only when they predominate is the tumor termed giant-cell sarcoma. These cells are large and contain several nuclei, which tend to arrange themselves together in the middle of the cell. The cytoplasm is opaque, and may contain fat vacuoles or erythrocytes. Spindle-cells make up the bulk of these tumors, which are usually very vascular.

TREATMENT

The results of treatment of retroperitoneal sarcomas have been most unsatisfactory, and the prognosis is unfavorable. Potassium iodid has been given internally, but without appreciable benefit. Coley's serum seems to have been of value in many cases as a palliative measure. Surgical removal has been the treatment of choice for years, but it is too often hampered by the location, size, infiltration, vascularity, and adherence to vital structures, preventing complete removal. The condition of twenty of the twenty-seven patients of the series operated on was found inoperable at the time of exploration. Seven tumors were enucleated or removed as thoroughly as possible; the tumor recurred in five instances; one patient died the day after operation; further data from the seventh could not be obtained.

The combination of radium and roentgen-ray treatment afforded excellent results in some of the cases. Several patients with both primary and secondary retroperitoneal sarcomas are now undergoing this type of treatment at the Clinic. The mass has entirely disappeared in several instances; the patients have gained weight and strength, and are able to carry on their work. It is too early to claim permanent cures in such conditions, but even if the great improvement is only temporary, it is well worth while, and achieves more than any previous treatment. If retroperitoneal sarcoma is suspected, a two weeks' course of radium and roentgen ray will be of great aid as a diagnostic measure. If the tumor is sarcoma, an appreciable diminution in size will be noted. If it is not sarcoma, no damage has been done and the mass may be explored. In this manner many patients may be saved the pain and expense of a fruitless operation and receive the benefit of the best treatment now at our command.

SUMMARY

1. Retroperitoneal sarcomas are seen often enough so that they should be constantly kept in mind in the diagnoses of abdominal disorders.

2. Trauma is apparently not a factor in the cause of retroperitoneal sarcoma.

3. Metastasis occurs in about 33 per cent of cases; it is most often found in the liver and lungs.

4. The most characteristic physical finding is the colon in a groove on the anterior surface of the tumor.

5. The small round-cell sarcoma or lymphosarcoma is the most common and most malignant type.

6. The prognosis is always unfavorable. A combination of radium and roentgen ray seems to be the most satisfactory treatment thus far instituted.

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II

UROGENITAL ORGANS

ABSORPTION FROM THE URINARY TRACT*

JAMES A. H. MAGOUN, Jr.

In this study experiments have been conducted for the purpose of determining whether certain dyes and bacteria can be absorbed from the pelvis of the kidney, the ureter, and the urethra. Dogs etherized at constant ether tension were used in all the experiments. Their conditions were kept as nearly normal as possible by the judicious use of heat, and so forth. In some of the experiments blood pressures were recorded. All operative manipulations were carried out with the minimum of trauma and hemorrhage. The dyes used included phenolsulphonephthalein and indigocarmin; these were recovered in the urine, collected from one or both ureters, depending on the nature of the experiment. The urine was collected in white porcelain dishes. One or two drops of sodium hydroxid, 25 per cent solution, was placed in each dish when phenolsulphonephthalein was employed. *Bacillus prodigiosus* was the bacteria chosen, because it is easily identified, because it probably never occurs spontaneously in the sites from which cultures were taken, and because it is rarely the cause of bacterial contamination in laboratories. The bacillus was grown in dextrose broth or washed from agar slants with sterile salt solution. The suspensions of dyes and bacteria were injected with a syringe, care being used to exert only the minimal amount of pressure. A careful record was kept of the time the dye was introduced, and the urine was tested repeatedly for the dye. When bacteria were used, the dogs were killed with ether at the end of from two to three hours, and cultures taken from the heart's blood, the lungs, liver, spleen, inferior vena cava opposite the renal vein, right kidney cortex and medulla, and left kidney cortex and medulla. The cultures were made by planting from 2 to 5 c.c. of blood and from 0.2 to 0.5 c.c. of the tissue juice of the various organs into tall tubes of glucose broth. The material from the tissues was obtained by aspirating the macerated particles and juice into sterile pipettes. The inoculated tubes were allowed to stand at room temperature for from forty-eight to ninety-six hours. The positive cultures were then plated on plain agar. In many of the experiments the fluid was warmed to 25° C. before injection. The absorption from the various components of the urinary system were considered separately.

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ABSORPTION FROM THE PELVIS OF THE KIDNEY

A dog was etherized and a low right rectus incision made. The right ureter was isolated and ligated at its juncture with the bladder. A small ureteral catheter was then placed in its upper portion and ligated there. The wound was closed. The animal was then turned on its right side and a left lumbar incision made. The left ureter was exposed at its juncture with the pelvis of the kidney. A small ureteral catheter was introduced into the pelvis and held there by a purse-string suture. Through this 1.5 c.c. of phenolsulphonephthalein was injected. The catheter was then withdrawn and the purse-string suture tied. Care was taken to avoid soiling and no appreciable pressure was used during injection. The urine collected from the right ureter gave the characteristic reaction in twenty minutes for phenolsulphonephthalein which continued to be excreted for a period of two hours. The experiment was not repeated because the results were conclusive and had been previously confirmed by Weld. I have demonstrated that bacteria may pass from the pelvis of the kidney into the blood stream, under conditions analogous to some of the states found clinically.

ABSORPTION FROM THE URETER

Two series of experiments were performed. In the first a right lumbar incision was made, exposing the ureter at its juncture with the pelvis of the kidney. A ligature of fine silk was then placed around the ureter at this point, care being taken to avoid injury to its blood supply. The wound was closed, the animal was turned on its back and a low right rectus incision made into the peritoneal cavity. The left ureter was isolated at its juncture with the bladder and a small ureteral catheter ligated in its upper portion. A ligature was placed around the lower right ureter (avoiding the blood supply), the ureter opened, a small ureteral catheter introduced for 1 to 2 cm. into its upper portion, and the ligature tightened around it, but not tied. Varying amounts of phenolsulphonephthalein or indigocarmin were then injected through the catheter. The catheter was removed and the ligature tied tightly. The operative area was well packed off to avoid soiling. The wound was closed. The urine from the left ureter was collected in the usual manner. Absorption occurred in six of the seven experiments.

In the second series bacteria were used, and a similar technic was employed, with the exception that the left ureter was not disturbed. Cultures were taken as usual. In only one of the five experiments were the organisms recovered, that is from the spleen and vena cava.

ABSORPTION FROM THE BLADDER

From a large series of experiments previously performed, dealing with the absorption of various dyes and the *Bacillus prodigiosus* from the bladder, it was found that the dyes were absorbed to a slight extent, while there was no absorption of bacteria.

ABSORPTION FROM THE URETHRA

Male dogs under constant ether anesthesia were employed. A low right rectus incision was made, the bladder was drawn up and a double ligature placed around the urethra at its juncture with the bladder. A small ureteral catheter was ligated in the upper portion of each ureter. The abdominal wound was closed. A purse-string suture was then placed around the external urethra and a No. 10 French soft rubber catheter introduced for about 1.5 cm. and the purse-string suture tightened on this. From 2 to 4 c.c. of the dye was injected slowly into the urethra through the catheter, with a minimal amount of pressure. The catheter was withdrawn and the purse-string suture tied. Care was taken to avoid soiling around the prepuce. The urine from both ureters was collected as usual. In four of the five experiments the phenolsulphonephthalein or indigocarmin appeared in the urine from one or both kidneys. In two of the four positive experiments the discrepancy in the time of appearance of the dye is probably owing to the delayed secretion of urine.

When bacteria were injected into the urethra, a similar technic was employed with the exception that the catheters were not placed in the ureters and that cultures were taken within two or three hours as in the preceding experiments. In only one of the five experiments were the bacteria recovered, and in this case they were found in the urine from the bladder.

DISCUSSION

These experiments demonstrate that the absorptive powers of the various portions of the urinary tract differ. The kidney absorbs dyes and bacteria to a marked extent. The ureter and urethra absorb the dyes readily, but bacteria less readily. The bladder, on the other hand, absorbs a very small amount of dye and no bacteria.

Absorption from the urinary tract is of importance clinically in several ways. The possibility that drugs introduced into the urethra, the ureter, or renal pelvis for whatever cause, may be absorbed and lead to dire results should always be borne in mind. It has been suggested that if the bladder is capable of absorbing to any great extent, the retention of the urine (containing the excreted dye) in the bladder for a period of two hours might lead to reabsorption of the urine and an unreliable phenolsulphonephthalein estimation. As it has been shown distinctly that the bladder has little absorbing power, this probably cannot occur. On the contrary, any lesion or deformity which would lead to retention of the dye-containing urine in the ureter or pelvis of the kidney, might result in the absorption of this urine and an apparent low phenolsulphonephthalein output. The following case is an example:

Case A359632. Mr. E. M., aged twenty-one years, came to the Clinic February 23, 1921, complaining of painless hematuria. At the onset of his illness, September, 1920, hematuria was slight and intermittent; recently it had been more severe and constant. For eight years the patient had had a slight dull backache referred to the lumbar area.

Roentgenograms revealed multiple shadows in the left kidney. On cystoscopic examination the catheter encountered obstruction in the left ureter 2 cm. above the orifice. There was no return of phenolsulphonephthalein from the left kidney. Operation revealed a large hydronephrotic sac, with a capacity of about 300 to 400 c.c. containing multiple round stones. Approximately one-half of the normal amount of kidney tissue remained; the ureter was not dilated.

In this case there was an indefinite form of obstruction at the ureteropelvic juncture. A large amount of renal tissue remained. The diminished output of the phenolsulphonephthalein in the presence of so large an amount of renal tissue, may be explained by (1) dilution of the dye by fluid in the renal pelvis, (2) reflex inhibition of secretion caused by the presence of the stones, and (3) the reabsorption of the dye from the pelvis of the kidney.

It has been suggested that in cases of pyelitis, the clinical phenomenon of chills and fever may be due to the absorption of urine and bacterial toxins. In the last few years the fact that the bacteria themselves may be absorbed from the urinary tract into the blood stream and result in a bacteremia has received more attention. Braasch has noted that reactions following cystoscopy occur much more often in male patients than in female. He attributes this to the absorption of bacteria through the prostatic urethra. Crabtree observed nine patients with hypertrophy of the prostate who were admitted to the hospital with sterile urine and then an inlying catheter was introduced. Blood cultures were taken during or soon after the chills which these patients developed. Organisms belonging to the colon group were recovered in seven of the nine cases. Crabtree believes that infection occurred by way of the prostate from infection of the prostatic urethra from the inlying catheter; he says, "One cannot deny that a pyelonephritis might be the source of a blood infection in the cases in which I have recovered the colon bacillus from the blood. Yet in the one case in which sufficient data was obtained to allow conclusions, blood infection was apparently primary."

Panton and Tidy recovered the colon bacillus from the blood of two patients who were apparently suffering from pyelonephritis. Kidd in discussing these cases, says, "Bacteria cannot be found in the blood except during the rigor in these cases of pyelitis. Further work is needed on this subject. I feel certain that it will be proved that rigor means in every case a temporary and cursory invasion of the blood stream with some microörganism." Braasch has found that patients occasionally develop chills and fever when a ureteral catheter is passed into the pelvis of the kidney. He assumes that, in this type of case, bacteria carried to the renal pelvis by the ureteral catheter may pass back through the kidney and infect the blood stream. I have taken cultures during chills in nine cases of pyelonephritis and one of epididymitis complicating prostatic hypertrophy. Organisms were recovered from the blood in six cases. In two the organism was definitely identified as the colon bacillus and one as *Bacillus pyocyaneus*. One was a gram-negative bacillus resembling the colon bacillus. Another was a diphtheroid gram-positive bacillus, and the last was *Staphylococcus albus*. The last two organisms were considered to be contaminations. There were four negative cultures including the one from the case of epididymitis.

No attempt has been made to study absorption under pathologic conditions, neither has the path by which absorption takes place been dealt with. In general, one may assume that the absorption occurs through the blood and lymphatics, the greater absorption through the former.

CONCLUSIONS

1. Certain dyes and bacteria can be absorbed from the normal kidney, ureters, and urethra.

2. A small amount of dye can be absorbed from the normal and acutely inflamed bladder.

3. Bacteria could not be recovered from the blood stream or various organs after injection into either the normal or acutely inflamed bladder.

4. In considering the relative absorbability, the kidney would seem to have the greatest absorptive power, with the urethra second and the ureter third.

5. It would appear that, both experimentally and clinically, bacteria may pass from the pelvis of the kidney into the blood.

6. In certain clinical cases the kidney, once infected, may act as a focus for a secondary bacteremia.

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THE ETIOLOGY OF URINARY LITHIASIS: A REVIEW AND AN EXPERIMENTAL STUDY*

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In a study of the literature on the etiology of urinary lithiasis and closely related subjects conclusions reached after careful analysis may be summarized briefly thus:

1. The problem of calculus formation in the urinary tract is one of chemical precipitation. The mechanism, which causes the precipitation of urates, oxalates, phosphates, and so forth, in such a way that a fused hard concretion arises, rather than the deposition of individual crystals which maintain a state of isolation in passing through the urinary tract, must be determined.

2. Differences in reaction as determined by the hydrogen ion concentration, and qualitative and quantitative changes in the urinary colloids (such as pigments, mucin, nebecula, albumin, and nucleoalbumin), have been shown to influence the nature of urinary sediments both chemically and physically. The microscopic and gross features of calculi would seem to show that an abnormal variation of these factors is at work in the formation of stone.

3. Race, age, heredity, trauma, occupation, diet, sex, and geographic distribution seem to suggest little with regard to the etiology of concrements; if factors at all, they are probably of secondary importance.

4. The three commonest diseases associated with an increase in the crystalline content of the urine, namely, gout, oxaluria, and phosphaturia are found far oftener without accompanying calculus deposition than with it. Many observers have assumed that there is a high incidence of lithiasis in such diseases, but have offered little statistical evidence to support their views.

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Xanthinuria and cystinuria are necessary to the formation of xanthin and cystin stones, but the frequency with which xanthinuric and cystinuric patients escape calculus formation is problematic.

5. On the whole, clinical evidence points to a local mechanism at work in the kidneys, ureters, or bladder to cause the stones. The common occurrence of demonstrable foci of infection in patients suffering from calculus, and the almost universal finding of infected kidneys or bladders associated with stone, lend weight to the belief that a specific stone-forming infection is at work in most instances. It is conceivable that at times excessive excretion of crystalloid material may reach such a degree that the normal protective colloids of the urine cannot handle the extra burden. Under such circumstances fusion of crystals and calculus formation might take place. Likewise, it is possible that qualitative or quantitative changes in the colloids of the urine may occur without bacterial infection. Such changes might lead to concrement formation even though the urinary crystalloid excretion remains within normal limits.

6. There is little direct evidence to prove that anatomic factors or stasis can initiate the stone-forming process, but their frequent association with calculus makes it seem likely that the stone-forming mechanism may work to better advantage under such circumstances.

The commoner theories of calculus formation were subjected to laboratory experimentation whenever possible, the procedure being guided to a great degree by the preceding studies.

SERIES I. THE EFFECT OF A HIGH CALCIUM DIET ON THE CRYSTALLINE CONTENT OF URINE

A high content of calcium in the diet has long been considered a factor predisposing to lithiasis. For this reason an effort was made to concentrate the calcium salts in the urine of rabbits by administering massive doses of calcium oxalate, chlorid, lactate, and phosphate to normal rabbits, and also to rabbits that had been subjected to a low-grade toxic nephritis by the administration of minute doses of oxalic acid, mercuric chlorid, cantharides, or chloroform.

It was found that forcing lime salts in massive doses under such conditions does not cause visible increase in the crystalline content of rabbits' urine or concrement formation. This is good evidence against a "hard water" or "lime soil" factor in the etiology of stone.

SERIES II. THE FORCED ADMINISTRATION OF OXALIC ACID AND ITS DERIVATIVES

Ebstein had shown that uric acid administered orally to rabbits and dogs is destroyed in the metabolism, but it had long been known that the administration of oxalic acid would cause the appearance of calcium oxalate in the urine. Therefore, in different groups of animals oxalic acid, sodium oxalate, and ammonium oxalate were fed in sublethal doses.

The octahedral form of calcium oxalate was found in the urine of these animals consistently, but no concretions or deposits were noted at necropsy. Toxic nephritis was present as a rule.

SERIES III. EFFECT OF ADMINISTRATION OF BUTYL OXALATE

Inasmuch as the oxaluria produced in Series II was not apparently intense, it was decided to feed an ester of oxalic acid in the hope that it would be less toxic than soluble oxalates, as it would furnish a lower concentration of oxalate ions. Ethyl oxalate, when given intramuscularly in doses of 0.5 c.c. or more, killed the animals almost immediately. Normal butyl oxalate was found less toxic and was therefore used in daily doses of 0.5 to 1 cc.. subcutaneously.

In one experiment, after the animal had received butyl oxalate and sodium oxalate daily for six days, it died spontaneously. Marked oxaluria with dumb-bell shaped crystals and atypical octahedra was noted. At necropsy the bladder contained about twenty small smooth white stones about 2 by 1 mm. in diameter. On chemical examination these proved to be calcium oxalate. As this was the first experiment of the series, cultures were not taken, and sections of the tissues were not made. The kidneys appeared slightly injected, but otherwise normal. All efforts to repeat the experiment proved futile until recently. Subsequent studies of this type of lithiasis will soon be published.

The association of an atypical crystalline oxaluria with formation of concretions was noted in one instance, while the remaining animals consistently showed a typical octahedral form of calcium oxalate in the urine with no concrement formation. This suggests that a change in crystalline form may be related to concrement formation.

SERIES IV. THE RESULT OF PLACING AN ORGANIC NUCLEUS IN THE RENAL PELVIS OF THE RABBIT

Pieces of kidney tissue excised and then carefully placed in the pelvis of the kidney uniformly showed disintegration without calcification.

Bits of muscle and fascia placed in the pelvis of the kidney in one instance became impregnated with lime salts, and infection was found.

It would seem that foreign bodies or organic nuclei in themselves will not initiate stone formation. If retained long enough, however, they may form a point of lowered resistance for bacterial invasion by irritation. Under such conditions they become impregnated with crystalline material which may develop into true calculus.

SERIES V. A STUDY OF THE FORMATION OF OXAMID CALCULI

The formation of concretions in the urinary tract after the administration of oxamid to animals had apparently been regarded as a medical curiosity since the time of Ebstein, although subsequently Tuffier and Rosenbach had carried out confirmatory experiments. Hence it was decided to study this phenomenon more in detail.

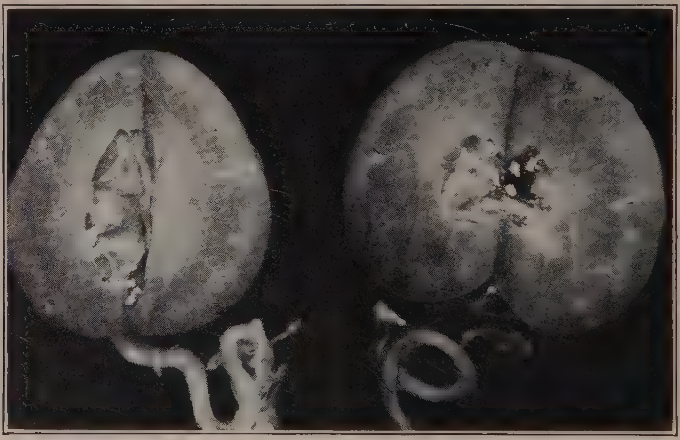

FIG. 61.—Experiment 61. Little tendency to fusion of crystals in urine of a rabbit fed oxamid. At necropsy there was no deposit in kidneys or bladder. (× 50.)

On feeding oxamid to rabbits and dogs sand was uniformly found in the urine; gravel deposits occurred in 75 per cent of the animals and stone in 50 per cent. The stones showed definite concentric striation. Cultures from the urine of the kidney and bladder were consistently sterile. The animals lost weight and died of toxic nephritis and hepatitis. The reaction of the urine, and the variations in dosage, and in duration of feeding within wide limits seemed not to produce quantitative change in the amount of oxamid deposit found in the urinary tract at necropsy (Fig. 61).

Crystallographic features of oxamid lithiasis.—Within twenty-four to thirty-six hours after administration of oxamid, abnormal crystals appeared in the urine. Pigmented crosses, simple and rough, squared forms and spheres occurred (Figs. 62–63). The sphere seemed to be

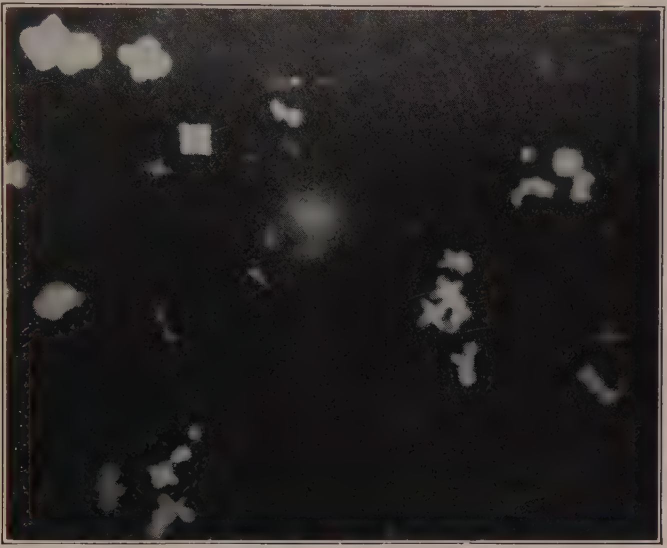

Fig. 62.—Experiment 68. A large agglomeration or beginning calculus composed of small spheres and crosses in urine of a rabbit fed on oxamid. (× 100.)

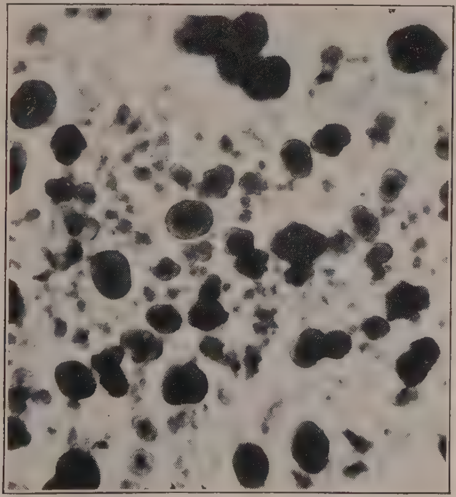

Fig. 63.—Experiment 68. Large smooth spheres showing a tendency to remain isolated from urine of a rabbit fed oxamid. (× 100.)

the end result of a series of phases of development from the simple cross. The larger cross-like forms and spheres tended to remain isolated. The smaller spherical forms were in all degrees of fusion and the calculi seemed to be made up of this variety.

Animals that had an abundance of the small fusing spherical crystals in their urine had stones more often than those whose urine abounded in the cross, squared, and intermediate forms.

The chemistry of oxamid. Its reactions in urine. Chemistry of oxamid stones.—Oxamid is the diamid of oxalic acid, $\begin{array}{l}CONH_2\\ |\\ CONH_2\end{array}$. It goes into solution slowly in boiling water, and is gradually hydrolyzed by further boiling to ammonium oxamate and later to ammonium oxalate. Acids or alkalis hasten this hydrolysis. As prepared synthetically by treating an oxalate ester with ammonia it consists of small, irregularly rhomboidal, fissured, translucent, colorless crystals which at times show split and roughened ends.

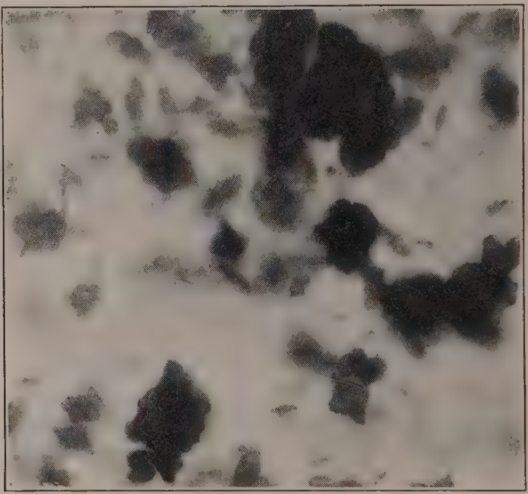

Fig. 64.—Deposit obtained when synthetic oxamid is dissolved in boiling urine and allowed to precipitate on cooling. The crystals are the developing-cross type; they are pigmented and show marked tendency to fuse into small agglomerations. This sediment is indistinguishable from that in the urine of rabbits fed on oxamid. (× 300.)

Oxamid stones give the reactions of oxamid, yielding ammonium and oxalate ions on prolonged boiling in water or on being dissolved in acid or alkali. They also contain an organic pigment, the identity of which has not been established.

On dissolving oxamid in urine, by heating a part is reprecipitated. This reprecipitated portion *in vitro* assumes a morphology entirely different from that of synthetic oxamid. The crystals are pigmented and all forms from the simple cross to the sphere have been noted under such conditions (Figs. 64–65). By repeating this process several times fusion of the spheroidal crystals has been noted and minute fragments, microscopically identical with small concrements obtained on feeding, have in this manner been produced in the test tube.

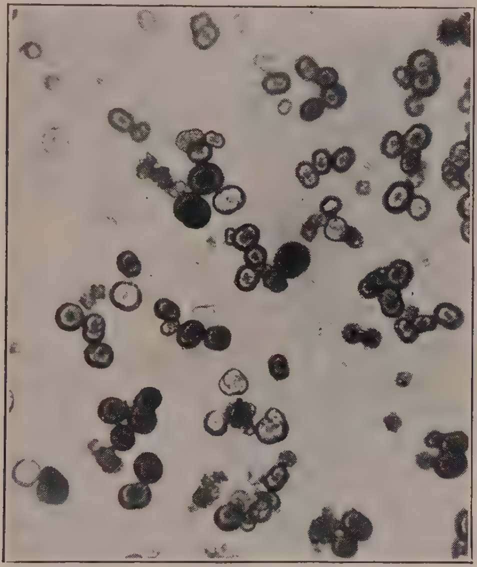

Fig. 65.—Oxamid crystals deposited *in vitro* from urine in which the synthetic chemical was dissolved by boiling. The perfect smooth sphere is shown here. There is no tendency to fusion. (× 200.)

Likewise solution of oxamid stones and filtrations through a heated charcoal filter result in extraction of the pigment and a change of morphology to a form nearly like that of synthetic oxamid.

The conclusion is drawn that the urinary colloids act on crystals of oxamid so as to transform them into fusing forms. This deduction is in harmony with experiments of Rainey, Ord and Shattock, and others on the relationship of colloids to morphology of crystalline form.

This suggests that abnormal colloids in urine may cause stones seen clinically.

SERIES VI. THE ANATOMIC FACTORS IN OXAMID LITHIASIS

1. It was shown that the first site of deposit of oxamid was along the line of insertion of the calices into the renal pelvis.

2. Roughening the renal pelvis by puncturing a number of times with a needle and then feeding oxamid over a period of weeks resulted in a greater deposit on the traumatized side.

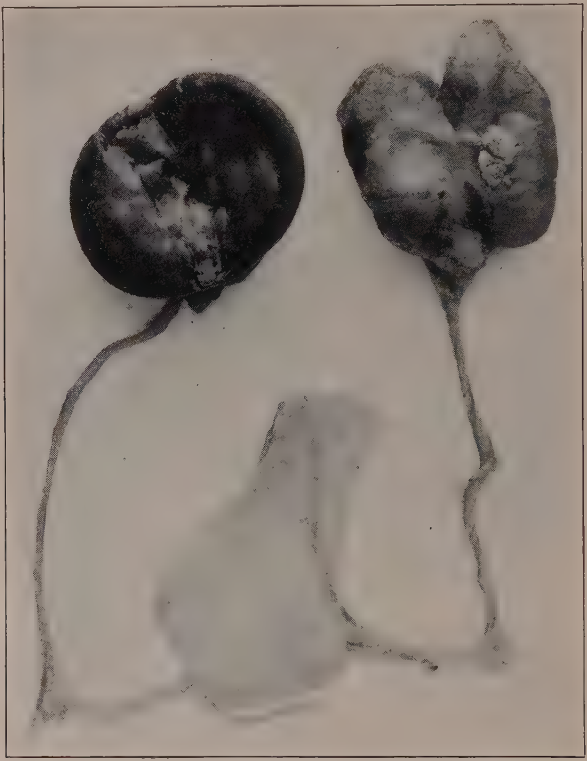

Fig. 66.—Experiment 90. Kidneys of a rabbit fed oxamid showing the formation of an oxamid calculus around an organic nucleus or foreign body (muscle tissue) previously placed in the left renal pelvis. A striking example of the rôle played by stasis, duplication of surfaces, and minute diverticula. The right untreated kidney is clear.

3. Slight constriction of the ureter produced by a rubber band brought about stone formation after feeding of oxamid in every case on the side with the constricted ureter. Stone formation in kidneys with unconstricted ureters occurred in only 50 per cent of the cases.

4. Placing of blood-vessel silk or pieces of muscle and fascia in the renal pelvis to act as nuclei, and feeding of oxamid was carried out.

Stone formation around the nucleus was consistently noted in such cases (Fig. 66).

Hence it was concluded that duplication of surfaces, diverticula, stasis, and hydronephrosis and nuclei, while not the cause of stone, greatly enhance the chances of retention of fusing crystals when these are present, and in this manner foster the formation of larger stones.

SERIES VII. THE INTRODUCTION OF INFLAMMATORY EXUDATES INTO THE URINARY STREAM BY MEANS OF EXPERIMENTAL RENAL INFECTION. THE INFLUENCE OF SUCH EXUDATES UPON THE DEPOSITION OF CALCIUM OXALATE AND THE PRODUCTION OF SMALL CONCRETIONS BY SUCH METHODS

Sodium oxalate 0.4 gm. was fed daily to rabbits. The octahedron form of calcium oxalate was noted in the urine. Infection of the kidney with colon bacilli (both fresh and old cultures) resulted in a change from the octahedral to atypical forms and in several instances minute concretions (circa 0.5 mm.) were found in the calices.

We explain this by assuming that bacterial exudates containing abnormal colloidal matter interfere with the protective colloids of the urine and cause them to lose their property of maintaining isolation of deposited crystals. A change in morphology to a fusing form occurs and concrement production takes place.

CONCLUSIONS FROM THE ENTIRE EXPERIMENTAL STUDY

The difficulty with which calcium salts, oxalates, urates, and other normal crystalline deposits of the urine are increased to any appreciable degree by various methods of administration has been pointed out. The only marked increase in visible crystals has been attained by feeding oxamid, a material foreign to the urine of animals. From this it would seem that an exogenous or dietary increase in crystalline materials would not produce a corresponding pathologic increase of these materials in the urine. On this basis, oxalurias, phosphaturias, xanthinurias, cystinurias, and excessive uric acid output must be more of endogenous than of exogenous origin. Some defect of metabolism by which the colloidal content or hydrogen ion concentration of the urine is altered, rather than a defect of diet, is at work.

Of the methods by which artificial concretions have been obtained, the feeding with oxamid only gave consistent results. There were suggestive features in connection with the other experiments which pointed to the working of some abnormal precipitation mechanism.

Oxamid, a crystalloid foreign to the urinary tract, on being excreted finds no mechanism present to keep its crystals separate as morphologic entities. Rather it is precipitated with colloidal material of normal urine in such a way that fusion of crystals and concrement formation ensues.

Mechanical factors are effective, at least, in the case of oxamid, in promoting retention of crystals and growth of the stones, but they are not essential to the process.

It is pointed out that four methods of protection against stone formation are: (1) natural defense against excessive concentration of urinary crystalloids, (2) protective colloids, which enable urine to carry water-insoluble urates, oxalates, and so forth, in solution, (3) the deposit of crystals as perfect isolated enfused units, probably also related to the protective colloids, and (4) the form and activity of the urinary tract. Calculi are probably due to abnormal colloidal matter in urine which interferes with the normal protective colloids.

Inflammatory exudates from clinical and experimental data seem the most likely source of the abnormal colloid. It is emphasized that not every inflammatory exudate produces stone. Neither does every abnormal colloid in urine, for pyelitis and nephritis are both remarkably free from concretions as a rule. This leads to the conclusion that stone-forming colloid must be specific and bacteria which produce it must be specific.

The possibility of stone being due to abnormal colloidal changes not associated with infection is emphasized. Thus over-concentration of urine with crystalline material or deficiency in urinary colloid might influence stone formation.

The rôle of the mechanical factors.—Stasis, surface duplication, organic nuclei, and diverticula do not lead to stone formation, but greatly favor stone growth when the conditions for lithiasis are present.

Clinical application.—The clinical application of this conception of calculus formation strengthens the experimental data. The stone-forming kidney becomes easily understood. The infected kidney pours abnormal colloids into the urine. These cause constant precipitation of crystalloids and fusion of the crystals precipitated. It may be seen readily why the removal of such a kidney is so seldom attended by recurrence of stone; why the recurrence of stone in the infected bladder is so frequent; why bad teeth and tonsillitis, conditions of lower nutrition states of inactivity, alcohol or carbohydrate fermentation in the stomach, and other conditions of lowered bodily resistance are accused by various, authors of playing a part in the process of lithiasis.

Difficulty is encountered when an attempt is made to explain the high incidence of stone in persons living in India and China, the association of uric acid gravel and uric acid infarcts in children, the alleged association of stone with previous injuries to the vertebral column and spinal cord, and other similar more obscure features of lithiasis. A tentative explanation is the fact that certain physical, climatic, geographic, or physiologic differences at times lower the resistance to stone-forming infections.

Attention should be called also to the occasional instances of spontaneous disintegration of calculi. Englisch collected more than 100 such cases which he considered authentic and a number of others which were questionable. This phenomenon has been explained as due to a resolution of the organic framework, or matrix of the stone. Rosenbach showed that the kidney stones of man placed in the renal pelvis of animals diminished in size. This suggests that solution of the organic matrix may take place under unusual circumstances.

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PROLONGED ANURIA. REPORT OF A CASE*

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Absolute retention, or anuria, producing an excess of the nitrogenous bodies in the blood gives a very different clinical picture from that in cases of uremia. In anuria the intellect is clear; there is an anorexia and a progressive stupor, but convulsive symptoms, edema, or gastro-intestinal upsets rarely occur.

In most cases of anuria one kidney is either destroyed or functionally useless. In reported cases proved at necropsy, it was found that one kidney was absent in nine, destroyed by stones in twenty-one, atrophied in eight, and the ureter was obliterated in six.

Morris reviewed forty-eight cases of anuria in which operation was not performed and forty-nine in which operation was performed; thirty-eight (79 per cent) of the forty-eight patients died and twenty-five (51 per cent) of the forty-nine recovered. A case of pure urinary poisoning resulting from a long standing complete obstruction of a single functioning kidney is reported.

REPORT OF CASE

Mrs. S. H. D., aged sixty years, was examined at the Mayo Clinic September 20, 1920. She had moderate dull pain in her left side for three months. She had lost 20 pounds in weight during the previous four months and there had been slight hematuria.

On cystoscopic examination neither meatus was seen, but a small inflammatory growth was found in the left base of the bladder. The urinary flow, which had been moderate for two months, suddenly stopped and no urine was passed for fourteen days, save at one urination when 25 c.c. was passed.

During this period the patient's intellect was perfectly clear and at most times she was quite comfortable. The blood urea gradually rose to 527 mg. for each 100 c.c. and the creatinin increased to 26.6 mg. There was no localizing evidence of obstruction to either kidney, but a bilateral exploration was done in an endeavor to find some mechanical cause of the anuria. The left kidney was found to be three times normal size, but not hydronephrotic; a decapsulation and pelviotomy were performed. The right kidney was small, sclerotic, and probably functionless. Following operation a large amount of urine drained from the left kidney. The blood urea dropped to 379 mg. and the creatinin to 20.3 mg. for each 100 c.c. The general condition of the patient improved for several days; but she died three days after operation.

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The lack of evidence pointing to the cause or location of the occlusion, a low function prior to the retention, and high blood nitrogen findings made surgical interference a last resort. An early operation would be desirable, if the obstruction were located or the nature of the process known.

THE EXTENSION OF HYPERNEPHROMA BY WAY OF THE RENAL VEIN*

LINWOOD D. KEYSER AND GORDON S. FOULDS

A hypernephromatous kidney with extension of the tumor into the renal vein was removed at the Mayo Clinic and offered an opportunity for a detailed pathologic study of the specimen with the hope of discovering, (1) the point at which the vein was invaded, (2) the manner of invasion, (3) the effect of the growth on the structure of the venous wall, and (4) whether or not the tumor had invaded other routes, such as the arterial or lymphatic.

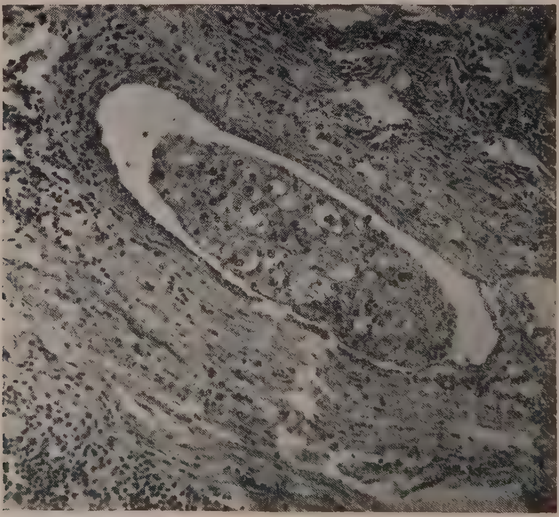

FIG. 67.—A small vessel near the hilum; probably a tiny venule. Typical hypernephroma tissue lies free in the lumen. (× 100.)

The entire upper pole of the kidney consisted of a mottled, yellowish, solid tumor traversed by fibrous bands which gave it a somewhat nodular appearance. A lappet of tumor tissue extended into the renal pelvis. The tumor showed typical hypernephroma morphology on microscopic section.

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* Abstract of paper published in the Journal of Urology, 1922, vii, 463–471. From the Section on Urology, Mayo Clinic.

The renal vein at the hilum was invaded by the growth. The renal artery and vein were dissected out to their terminal ramifications which entered the walls of the renal sinus. Blocks of tissue which included these ramifications for a distance of 1 cm. into the substance of the kidney were excised. A number of sections from artery and vein at different points in their course from the kidney outward were studied. The arteries showed nothing unusual. Cross sections of the renal vein, however, showed some interesting phases of the extension of hypernephroma by this route.

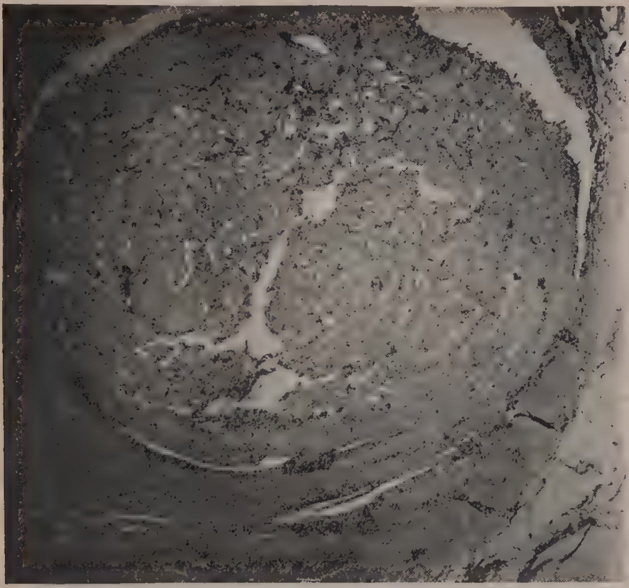

FIG. 68.—A large vein just beyond the hilum. Thin walls and lumen filled with tumor tissue are noteworthy features. (× 18.)

A section taken from the renal tissue at the point of emergence of one of the smaller radicles of the renal vein (Fig. 67) contained a small vessel 0.5 by 0.1 mm. lined by endothelium and with a definite wall of fibrous tissue separating it from the surrounding tumor tissue. No muscle elements could be made out and there was no internal elastic membrane. Hence the structure was either a venule or lymph vessel, probably the former. The lumen of the vessel was filled with free lying tissue which consisted of cells and stroma identical in morphology with that of the tumor tissue seen elsewhere. A number of sections through this block showed that the endothelial wall of the vessel remained undisturbed and uninvaded by the tissue growth.

A somewhat larger venous branch is shown in Figure 68. The lumen of this was likewise filled with a solid mass of hypernephroma tissue, and while the endothelium of the wall had been destroyed there seemed to be no active mural invasion by the neoplasm. The vein, however, had been markedly dilated and its walls thinned by the pressure of the growth. A section from the wall of the main renal vein also showed the lumen to be filled with hypernephroma tissue and the thin wall infiltrated at various points with lymphocytes, although no definite hypernephroma cells were found outside the lumen proper. Numerous sections were made at various points along the venous branches. All showed essentially the same characteristic. The lumina were filled with the mass, but there was little tendency for the growth to invade or perforate the venous wall.

Study of the intrinsic renal lymphatics failed to reveal any hypernephroma cells in the lymph spaces or other evidence of extension by their route.

DISCUSSION

The extension of hypernephroma into the renal vein has long been recognized, and according to most observers metastasis to the liver, lungs, and bones is brought about in this manner.

All authors are agreed that extension by way of the lymphatics is much less common.

Metastasis from hypernephroma may affect any organ and the very multiplicity of tissues involved secondarily suggests that the blood stream is, as a rule, the path of distribution. Metastasis may be found when the renal tumor is so small that it cannot be palpated clinically and microscopic sections of superficial tumors may be the first to direct attention to the existence of the primary renal growth. Extension by way of the renal arteries is extremely rare if it occurs at all. This will be readily understood if it is considered that under such conditions the growth would have to extend in opposition to the pressure of the arterial current.

Our studies seem to show that, as a rule, hypernephroma enters venules and grows forward into the venous lumina. In its extension it exhibits little tendency to invade or perforate the venous wall which however, loses its endothelium and becomes thinned out in places from the pressure atrophy produced by the growing mass. It is easily understood how minute emboli may break off from time to time and be carried by the venous stream to the lungs. Here the cells are arrested or pass on through the capillary bed to the general circulation. Thus metastasis to the bones and other remote tissues occurs. It is suggested by Councilman and MacCallum that the involvement of lymph nodes anatomically unrelated to the kidney primarily involved may occur secondarily from metastatic growths disseminated by way of the blood stream.

AN EXPERIMENTAL STUDY OF THE URETER AFTER NEPHRECTOMY: REPORT OF A CLINICAL CASE OF PYO-URETER*

RAYMOND L. LATCHEM

This study was undertaken in order to investigate the ultimate fate of the ureter after nephrectomy. Experiments were planned to simulate, as closely as possible, the conditions found in clinical cases in which nephrectomy is performed, and either a normal ureter, a hydro-ureter, or a pyo-ureter (infected hydro-ureter) is left undisturbed. A few experiments were performed leaving the normal ureter in place in order to determine the natural trend of events in the healthy organ after nephrectomy and to have a basis of comparison for the diseased ureters. It was believed that the experiments with hydro-ureters, infected and uninfected, might have some clinical importance, as such ureters are constantly being left in the body after nephrectomy. For example, ureteral calculus often produces hydro-ureter and hydronephrosis, but probably rarely causes complete blocking of the ureteral contents, and permits drainage of the ureter after nephrectomy. Complete blockage of ureteral contents occurs following ligature of the ureter with silk during operations, such as resection of the bladder and colon for cancer and may accidentally occur with catgut in operations in the pelvis. A certain percentage of such tied-off kidneys produce acute surgical conditions necessitating removal of the organ, especially if it was the site of infection before ligation. The ureter in such cases is always slightly enlarged and full of fluid which will never have an opportunity to escape naturally.

In order to produce the hydro-ureters it was necessary to obstruct the outflow of urine from one kidney and cause hydronephrosis; thus considerable data was secured which simply confirmed the work of others in regard to this process. The effect on the kidney of complete obstruction of the ureter has been studied, and full corroboratory accounts of such work have been published by Barney, Keith and Pulford, Reid, Johnson, Caulk, Harrington, and others. This phase of the subject will not, therefore, be discussed.

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* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Urology, 1922. Published in the Journal of Urology, 1922, viii, 257–279. From the Sections on Experimental Surgery and Urology, Mayo Clinic.

Experimental work on the ureter has been confined mainly to ligation and its effect on the kidney, and to transplantations. Caulk's work was undertaken primarily to establish the length of time a kidney could be obstructed completely and still resume function and to determine the length of time necessary for the absorption of the plain catgut causing the obstruction, and the length of time before the lumen of the ureter reopened. It was shown that the catgut was absorbed in about three weeks and the lumen of the ureter was open in from six to eight weeks sufficiently to drain the urine freely. The kidney, meanwhile, unless nephrostomized, would be past the point of maintaining function. Johnson had previously demonstrated that if obstruction had not lasted more than two weeks function might possibly return to normal, and the longer the period of obstruction, the slower the rate of recovery.

Dogs were used in all the experiments because of the similarity of the anatomy, the physiology, and the blood supply to that of man. Surgical procedures were carried out with the strictest observance of aseptic technic. The operative area was prepared by shaving, thorough cleansing with benzene and alcohol, and two coats of iodin (10 per cent). The animals were anesthetized with ether. The technic of the various surgical procedures is discussed briefly under each group of experiments; the peritoneum and fascia were closed with catgut, and the skin closed with linen and a protective dressing and sealed with collodion. The animals were kept under conditions most favorable for health and comfort. The material studied has been classified in three groups:

Group 1. Nephrectomy; a normal ureter remaining.

Group 2. Nephrectomy; a hydro-ureter or pyo-ureter, with (1) a patent lumen, or (2) a completely obstructed lumen remaining.

Group 3. Control group; a hydro-ureter or pyo-ureter produced without nephrectomy, but with (1) ureteral obstruction removed, or (2) ureteral obstruction not removed.

Group 1.—Left nephrectomies were performed on three dogs and they were allowed to live as long as possible (Table 1). In each case at necropsy the ureter, which had been deprived of its normal function of conveying urine, was found patent, and in two instances noticeably smaller than its mate. Sections from the same level of both ureters were studied microscopically. It was impossible to detect any difference in the mucosa of the right and left ureters, or in the fibrous coats. However, a comparison of the muscular layers revealed a definite diminution of the amount of muscular tissue in the functionless ureters (Figs. 69, 70). From these observations it may be deduced that no attempt is made toward obliteration of the lumen of the normal ureter after nephrectomy, but that the muscular coat becomes atrophied.

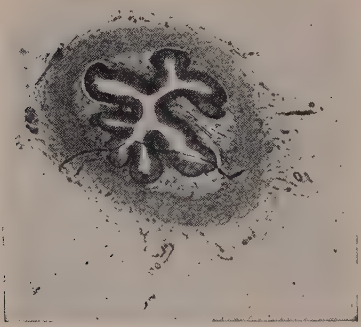

Fig. 69.

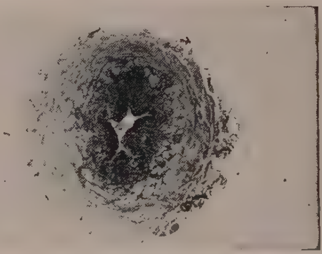

Fig. 70.

Fig. 69.—Experiment 671. Normal right ureter. (× 14.)

Fig. 70.—Experiment 671. Left ureter, showing muscular atrophy and normal mucous membrane. (× 14.)

TABLE 1

Group 1. Normal Ureter After Nephrectomy

Experiment, 1919.	Nephrectomy.	Duration of experiment, days.	Necropsy findings.
671	10–7	480	Right kidney enlarged almost one-third more than normal; right ureter normal. Left ureter apparently normal, catheter passed equally as well as in the right ureter. Necropsy 54 (1921).
674	10–7	275	Right kidney and ureter normal. Left ureter thinner walled than the right and without the "feel" of normal tissue as in the right. Lumen patent. Necropsy 331 (1920).
677	10–9	405	Right kidney somewhat enlarged, right ureter normal. Left ureter smaller than the right with patent lumen. Necropsy 593 (1920).

Group 2.—One ureter was ligated in each of twelve dogs at a point 2.5 cm. above the bladder with catgut (chromic No. 2) applied so as to

facilitate removal later. It was found that if a small section of a small urethral catheter was split and placed around the ureter with the ligature tightened over it, later removal was much easier than if the ligature was applied directly to the ureter. In about two weeks the ligature around the ureter was carefully removed, the condition of the ureter noted, and the kidney on that side excised. The object of this series of experiments was to produce in each case a ureter such as would be present in hydronephrosis or pyonephrosis due to obstruction low in the ureter and, if possible, to produce a ureter that would drain following removal of the obstruction. In performing the nephrectomy the upper ureter was ligated twice with silk and severed between the ligatures, so that its contents would not be lost. In four of the experiments pure cultures of staphylococci were introduced into the distended ureter.

At necropsy in six of these animals (Table 2) it was found that the ureteral obstruction had either been relieved at the time the ligature was removed, or that the lumen had opened subsequently, as the ureters were empty and it was possible to demonstrate a lumen at the point of ligation. In only one animal, however, was the ureter normal throughout in size. In the other five animals there was a varying degree of obstruction with reduction in the size of the lumen which allowed the passage of fluid, but denied, in some cases, the passage of a ureteral catheter. These cases might be compared to surgical cases in which a hydronephrotic kidney was removed, secondary to a stone in the ureter, leaving a hydro-ureter with a calculus in its lower portion which did not cause complete obstruction.

In the five animals the size of the ureter above the point of ligation was from two to three times that of its mate, and hypertrophy of the ureter, as a whole, could be made out grossly, while below the point of ligation the ureters were normal. On microscopic examination the increase in the size of the ureteral wall was found to be owing to actual increase in the amount of muscular tissue, the increase being chiefly confined to the circular layer, but also demonstrable in the longitudinal layers. That there was an actual increase in muscle tissue could be appreciated by comparing the thickness of the muscle layer in the diseased ureter with that of its mate, and by taking into consideration the increased size of the one over the other. For example, in Experiment 695 the thickness of the muscle wall of the left ureter is greater than that of the right and the diameter of the left ureter is several times that of the right (Figs. 71, 72). The greater amount of hypertrophy or increase

TABLE 2

HYDRO-URETER, WITH DRAINAGE OF CONTENTS, AT VARIOUS PERIODS AFTER NEPHRECTOMY

Experiment, 1919.	Ureter ligated.	Ligature removed and nephrectomy.	Condition of ureter and kidney.	Duration of experiment, days.	Necropsy findings.
695	10–14	10–30	Tortuous hydro-ureter above ligature, normal below. Hydronephrosis.	60	Necropsy 617. Right kidney and ureter below ligation normal. Left ureter above ligation enlarged and cord-like. Lumen open to fluid.
713	10–21	11–6	Tortuous hydro-ureter above ligature, normal below. Hydronephrosis.	315	Necropsy 445. Slight hypertrophy of the left kidney. Left ureter normal. Right ureter slightly larger above ligation than below. Lumen patent.
694	10–14	10–30	Tortuous hydro-ureter above ligature, normal below. Hydronephrosis.	65	Necropsy 627. Right kidney and ureter normal. Left ureter cord-like and slightly larger above ligation than below.
782	10–18	12–2	Very large tortuous hydro-ureter. Large hydronephrosis.	239	Necropsy 339. Right kidney and ureter normal. Left ureter apparently normal. Lumen patent and free of any obstruction.
700	10–16	11–6	Large hydro-ureter and hydronephrosis.	167	Necropsy 145. Right kidney, acute nephritis; right ureter normal. Left ureter enlarged above ligation, normal below. Lumen obstructed, but patent.
714	10–21	11–4	Large hydro-ureter and hydronephrosis. Culture of staphylococcus introduced into distended ureter.	87	Necropsy 19 (1920). Right kidney and ureter normal. Left ureter almost twice size of right, but lumen patent.

in muscular tissue, as compared with its mate, was observed in the animals coming to necropsy after the shorter periods and was less pronounced in those that lived longer, as in Experiments 713 and 782. This indicates that after the obstruction is removed, which provides the stimulus to muscular hypertrophy, the muscular coat gradually atrophies. This had evidently occurred in Experiment 782 in which obstruction to the lumen could not be demonstrated; the two ureters were apparently the same size although still showing microscopically a slight increase of muscle tissue in the ureter that had been obstructed.

Except for the "ironing out" of the mucosal folds to a varying degree in each instance, the mucous membrane appeared normal. There was no demonstrable change in the fibrous coat and none in the submucosa, except in one case (Experiment 713) in which there was lymphocytic infiltration and slight connective tissue formation. In no case was there peri-urethral inflammation, either active or old, as would be indicated by adhesions. The staphylococci introduced into the ureteral contents in the one case had evidently drained out with the fluid and did not cause inflammation. These findings indicate that a hypertrophic hydro-ureter with incomplete obstruction to its lumen will, after nephrectomy, empty itself and gradually become atrophic in the muscular layer. It will preserve a normal mucous membrane, and will not cause irritation outside its walls.

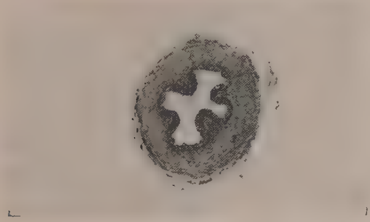

FIG. 71.

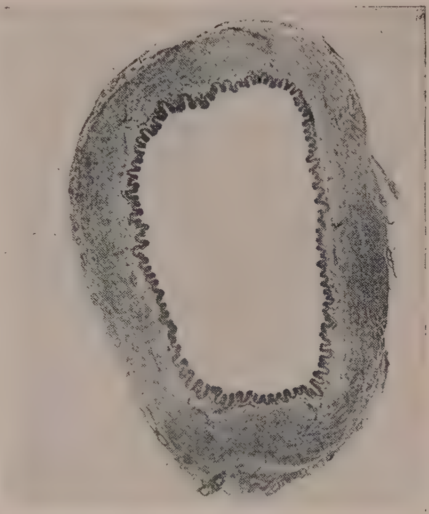

FIG. 72.

FIG. 71.—Experiment 695. Normal right ureter. (× 14.)

FIG. 72.—Experiment 695. Left ureter, showing normal mucosa and hypertrophic musculature. (× 14.)

The ureters of the remaining six animals (Table 3) were all completely obstructed at the point of ligation, thus approximating the surgical cases of complete obstruction to a hydro-ureter or pyo-ureter after nephrectomy. All of the ureters were distended, three with clear fluid and three with pus. Those containing pus were surrounded by adhesions, and it was difficult to remove them from their beds. In one case

TABLE 3

Hydro-ureter and Pyo-ureter, with Complete Obstruction to Drainage of Contents at Various Periods After Nephrectomy

Experiment, 1919.	Ureter ligated.	Ligature removed; nephrectomy.	Condition of ureter and kidney.	Duration of experiment, days.	Necropsy findings.
598	10–16	11–20	Large tortuous hydro-ureter. Large hydronephrosis.	375	Necropsy 549 (1920). Right kidney one-third larger than normal, ureter normal. Large dilated left ureter tortuous and full of pus. Complete obstruction at point of ligation, normal below. Ureter surrounded by dense adhesions.
732	10–28	11–12	Hydro-ureter and hydronephrosis. Culture of staphylococci introduced into ureter.	28	Necropsy 567. Right kidney and ureter normal. Left ureter distended with pus. Abscess around lower ureter.
717	10–23	11–11	Large hydro-ureter and hydronephrosis.	46	Necropsy 717. Right kidney and ureter normal. Left ureter twice the size of the right and full of clear fluid. Complete stenosis of lumen.
734	10–28	11–12	Tortuous hydro-ureter and hydronephrosis.	35	Necropsy 589. Right kidney and ureter normal. Left kidney distended with clear fluid as at previous operation. Complete stenosis of lumen.
733	10–28	11–12	Large hydro-ureter.	106	Necropsy 70 (1920). Right kidney and ureter normal. Left ureter about four times normal size and distended with clear fluid. Complete stenosis of lumen.
699	10–16	11–4	Large hydro-ureter and hydronephrosis. Culture of staphylococci introduced into ureter.	357	Necropsy 512 (1920). Right kidney showed chronic nephritis; right ureter normal. Left ureter large, hard, contained turbid fluid, and was surrounded by firm adhesions. Complete obstruction.

the pus had ruptured through and caused an abscess. The ureters were enlarged above the point of constriction from three to five times the size of their mates, and were normal below that point.

Microscopic examination revealed flattened mucosa, even to complete obliteration of the mucosal folds; it was otherwise normal. The submucosa was normal in the uninfected cases, but in the infected cases showed lymphocytic and leukocytic infiltration, which in one instance extended into the muscular layer. The muscular layer was markedly increased in all, and more increase of the longitudinal muscles was noted than in the previous ureters examined (Figs. 73, 74). Increase in longitudinal muscle was noted especially in the ureters of animals that lived longest (Experiments 598 and 699), although the circular coat still predominated. This may indicate that hypertrophy occurs first in the circular layers and later in the longitudinal. In all of the cases the muscular hypertrophy was more pronounced than in the group in which the ureter had drained, indicating that the muscle increased somewhat after nephrectomy and did not atrophy as long as the ureter contained fluid.

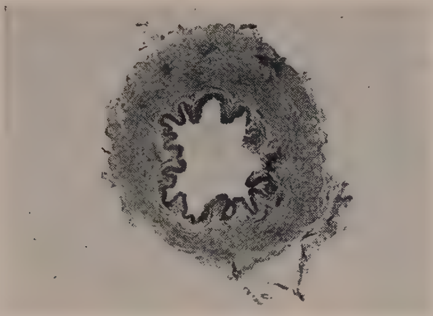

FIG. 73.—Experiment 598. Normal right ureter. (× 14.)

The most striking feature at necropsy in these cases was the distention of the ureter with fluid. The three uninfected hydro-ureters were apparently in the same condition as when ligated and dropped back after nephrectomy. The three infected hydro-ureters, two of which had been deliberately infected at the time of nephrectomy, showed definite inflammatory reaction with infiltration of leukocytes into the submucosa and outer fibrous coat (Fig. 74), and the formation of connective tissue adhesions around the ureter. In one instance the organism penetrated the wall of the ureter and a peri-ureteral abscess resulted.

From these results it would seem that after nephrectomy in cases of hydro-ureter and pyo-ureter in which there is complete obstruction, absorption, if occurring at all, would be very slow and with the additional danger, in the infected cases, of the infection extending through the ureter. In this group, also, the mucous membrane remained intact, but the muscular coat remained hypertrophic.

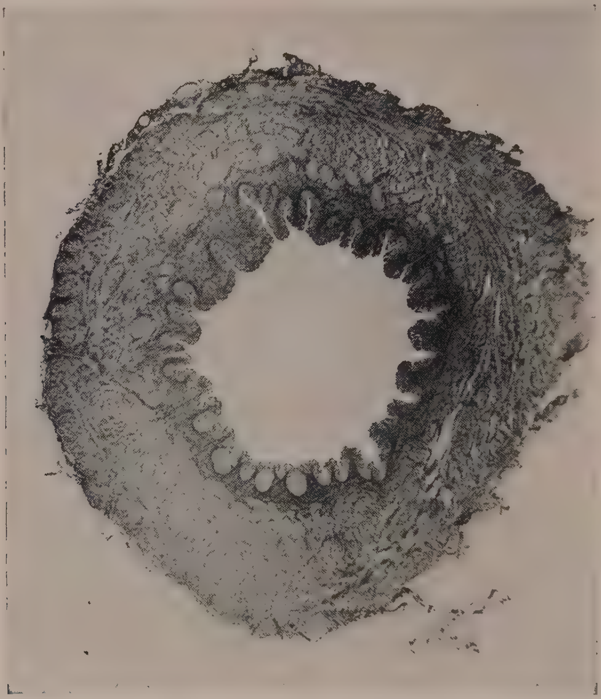

Fig. 74.—Experiment 598. Left ureter showing muscular hypertrophy, normal mucosa, and peri-ureteritis. (× 14.)

Group 3.—The ureter was ligated in nine animals, but nephrectomy was not performed later. The obstruction to the ureter was successfully removed in two cases, not attempted in four, and failed to be removed in three. These experiments were performed for the purpose of establishing controls on the results obtained in Group 2.

In the two instances in which hydro-ureter and hydronephrosis were produced and the obstruction to the ureter removed fourteen days later, without nephrectomy, the animals lived for a long time (Table 4)

TABLE 4

Hydro-ureter, with Free Drainage and Without Nephrectomy

Experiment, 1919.	Ureter ligated.	Ligature removed.	Condition of operated ureter and kidney.	Duration of experiment, days.	Necropsy findings.
693	10–14	10–28	Large hydro-ureter. Hydronephrosis.	325	Necropsy 444 (1920). Right kidney slightly enlarged, ureter normal. Left kidney smaller than normal; slightly hydronephrotic. Left ureter thickened and enlarged at point of ligation, slightly enlarged above and normal below. Lumen at point of ligation very small but patent.
712	10–21	11–4	Ureter dilated and tortuous. Hydronephrosis.	340	Necropsy 490 (1920). Right kidney and ureter normal. Left kidney but slightly smaller than the right and, on cut section, presented no gross difference from the right aside from a slight enlargement of the pelvis. Left ureter slightly larger than right, except at point of ligation where it was definitely thicker. It was impossible to pass a ureteral catheter either up or down the ureter past this point, but fluid passed through without difficulty. Judging from gross appearance the kidneys had equal function.

and the results were sufficiently interesting to record. The period of obstruction was the same in each instance and presumably the amount of damage to the kidney the same. In each instance, after the removal of the obstruction, the kidney resumed function and the degree of recovery was evidently affected by the condition of the ureter, as in one case there was partial obstruction of the lumen and in the other an unobstructed channel. As the result of the partial obstruction in Experiment 693 (Table 4) the ureter was hypertrophic and there was slight hydronephrosis with some atrophy of the substance of the kidney.

Microscopic examination of the effected kidney showed normal glomeruli and tubules and also areas of intertubular connective tissue formation, while the muscular coat of a hypertrophic ureter was developed at least one-third more than that of its mate. In Experiment 712 (Fig. 75)

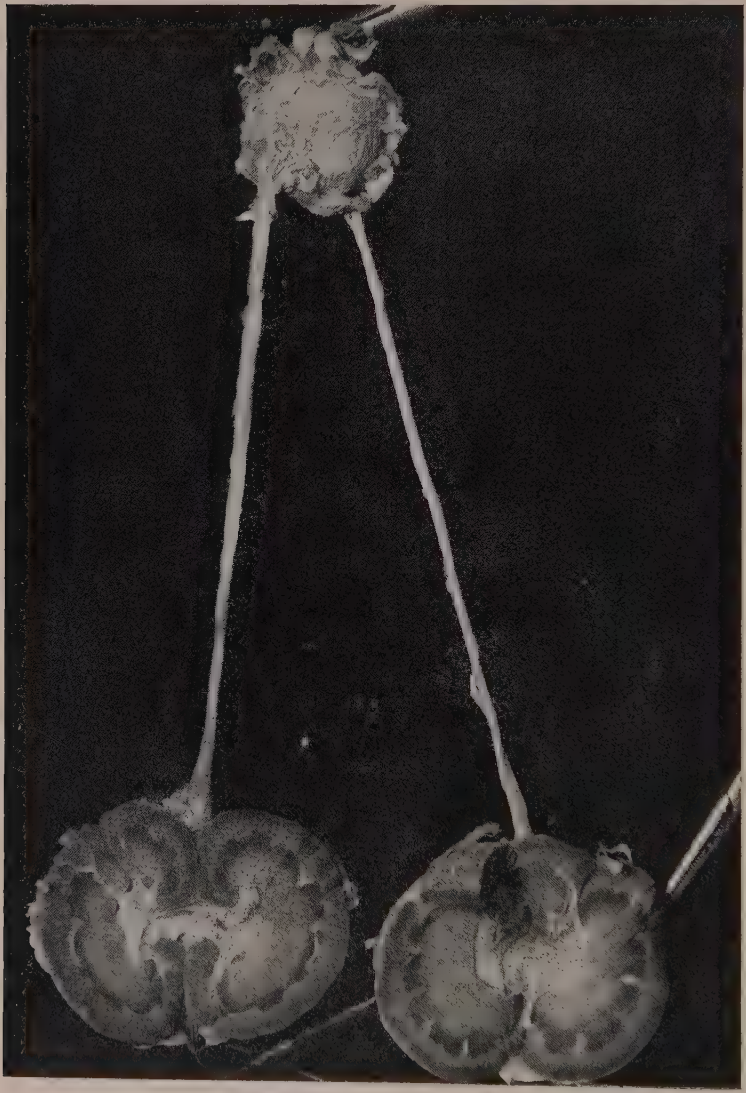

FIG. 75.—Experiment 712. Kidneys, ureters, and bladder.

the ureteral lumen was unobstructed, and it was difficult to determine grossly or microscopically a difference in the substance of the kidneys, but the lumen of the left ureter was slightly larger than that of the right, although the muscle coats were equally developed. These results were interesting in that they confirmed previous reports of the return of renal function, providing damage by obstruction to the outflow of urine is not irreparable. From the condition of the ureters it seems that muscular hypertrophy produced by obstruction tends to disappear after the obstruction is removed.

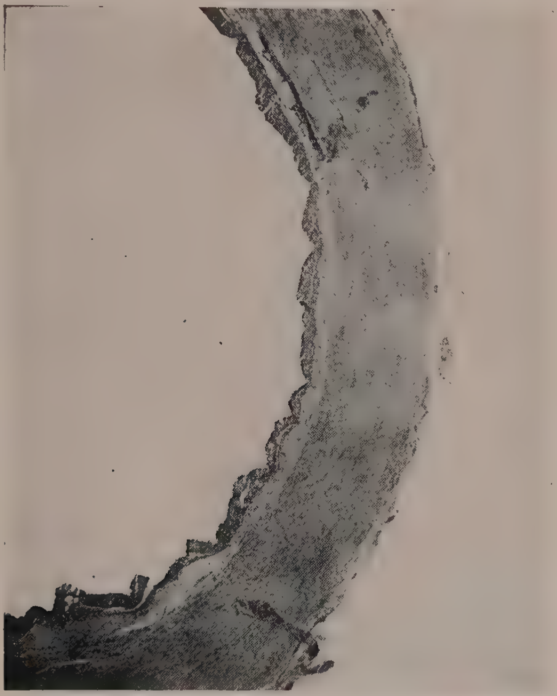

FIG. 76.—Experiment 679. Section of wall of left ureter, showing muscular hypertrophy. (× 14.)

The remaining seven experiments in Group 3 without later nephrectomy consisted of one in which the ureter was ligated at a point 5 cm. below the pelvis of the kidney, two in which one ureter was crushed and ligated at a point just above the bladder, and four in which the attempt to remove the ligature, previously placed on the ureter, failed (Table 5). The hypertrophy of which the muscular wall of the ureter is capable is illustrated by these experiments (Fig. 76), as in all but one

TABLE 5

HYDRO-URETER AND PYO-URETER WITH COMPLETE OBSTRUCTION TO DRAINAGE OF CONTENTS AND WITHOUT NEPHRECTOMY

Experiment, 1919.	Ureter ligated.	Ligature not removed or failed to be removed.	Condition of ureter and kidney operated on.	Duration of experiment, days.	Necropsy findings.
672	10–7	.....	Ureter crushed and ligated.	72	Necropsy 626. Right kidney and ureter normal. Left kidney a large hydronephrotic sac. Left ureter tortuous and dilated above ligation, normal below.
701	10–16	.....	Ureter crushed and ligated.	17	Necropsy 494. Right kidney and ureter normal. Large hydronephrosis of left kidney which had ruptured into the perirenal fascia where there was a large collection of urine. Left ureter dilated above point of ligation, normal below.
678	10–9	.....	Ureter ligated 5 cm. below pelvis of kidney. No attempt to remove it.	480	Necropsy 34 (1920). Right kidney slightly enlarged with normal ureter. Left kidney and its pelvis formed a large sac measuring 8 by 12 by 16 cm. and filled with clear fluid. Left ureter from sac to point of ligation was very tortuous and measured 12.5 cm. Left ureter normal below the point of ligation.
781	11–18	12–2	Unable to remove the ligature. Hydronephrosis and hydro-ureter. Re-ligated ureter.	93	Necropsy 82 (1920). Right kidney and ureter normal. Left kidney a shell slightly smaller than right kidney and filled with pus. Left ureter 1 cm. in diameter and filled with pus. Abscess around the lower portion of the ureter.
718	10–23	11–11	Ureter three times normal size. Hydronephrosis. Unable to remove ligature; re-ligated and dropped back.	360	Necropsy 525 (1920). Right kidney and ureter normal. Left kidney was one-half the size of the right, with a thin cortex of renal tissue and full of cloudy fluid. Both kidney and ureter were matted in adhesions. Left ureter enlarged and tortuous to point of ligation, normal below. Impossible to demonstrate lumen at point of ligation. Condition evidently infected hydronephrosis with perinephritis infection, and partial absorption of the contents of the kidney.
780	11–18	12–2	Hydro-ureter and hydronephrosis. Ligature could not be removed; ureter re-ligated and returned.	310	Necropsy 489 (1920). Right kidney and ureter normal. Large uninfected hydronephrosis on left with large dilated ureter.
679	10–8	10–23	Large tortuous hydro-ureter and large hydronephrosis. Ligature could not be removed.	180	Necropsy 155 (1920). Right kidney and ureter normal. Large infected hydronephrosis on left with a large ureter also full of pus. Marked perinephritis infection.

animal that lived only seventeen days the ureter was dilated and tortuous and greater increase of the muscle layer was found than in ureters previously examined. In this group also the animals that lived the longest had a greater increase in the longitudinal muscle bands, although the circular layer always predominated. In no case, however, was this hypertrophy equal to the hypertrophy of the ureter usually observed in cases of ureteral obstruction with a functioning kidney. The

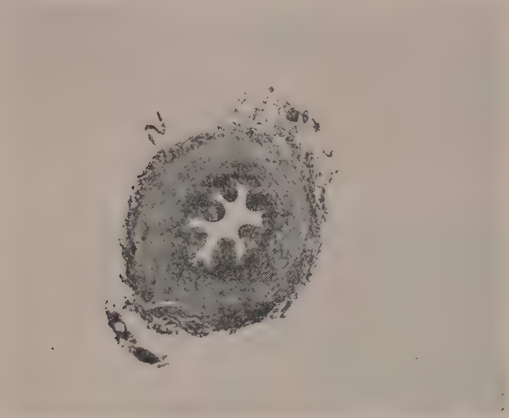

FIG. 77.—Experiment 678. Normal right ureter. (X 14.)

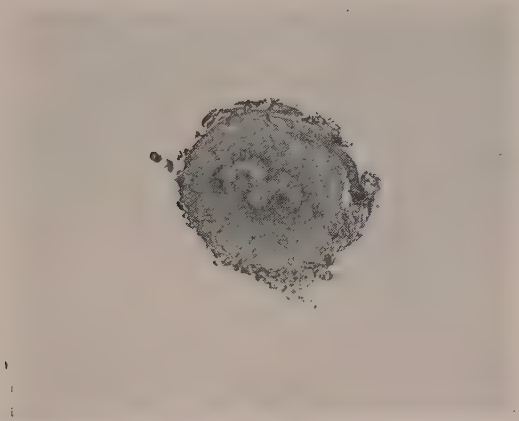

FIG. 78.—Experiment 678. Left ureter below point of complete obstruction, showing normal mucosa and musculature. (X 14.)

results in Experiment 678, in which the ureter was ligated at a point 5 cm. below the pelvis of the kidney, were very interesting in that the ureter was normal below the point of ligation and did not show atrophic tendencies, but was greatly hypertrophic above the point of ligation (Figs. 77, 78, 79, and 80). The mucous membrane, except for the obliteration of the mucosal folds by the distention of the ureter, was normal in every case, including those that were infected.

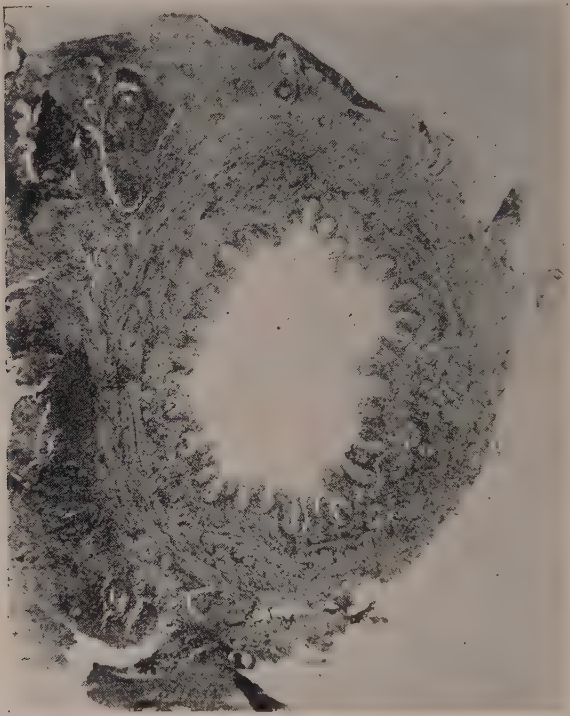

Fig. 79.—Experiment 678. Left ureter above point of complete obstruction, showing normal mucosa and marked hypertrophy of the muscle layers. (× 14.)

Besides the experiments tabulated there were four in each of which one ureter was ligated. One of the animals died on the eighth day from a badly infected wound, two on the twenty-seventh and thirtieth days respectively from distemper and pneumonia, and one the fourteenth day from the anesthetic, while preparations were being made to remove the ligature around the ureter. All of these showed the usual hydronephrosis and hydro-ureter.

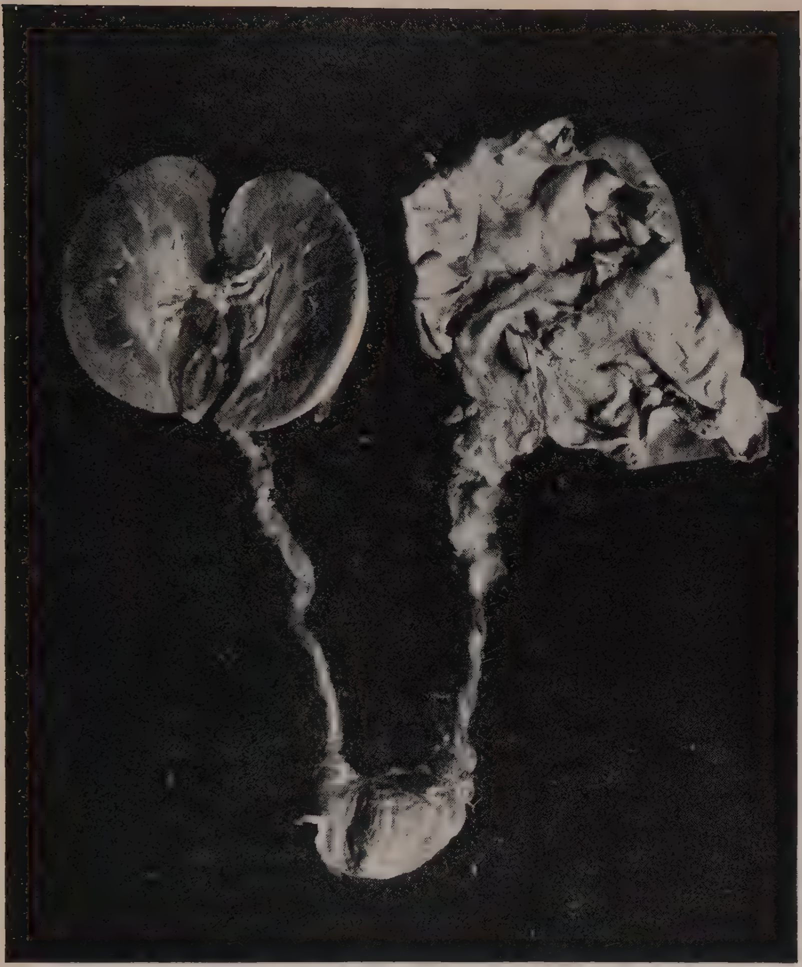

Fig. 80.—Experiment 678. Right kidney, left hydronephrotic sac, both ureters and bladder.

REPORT OF A CLINICAL CASE OF PYO-URETER

That a diseased ureter can cause later complications after nephrectomy has been recognized by urologists, although reports of cases seem to be difficult to obtain. Fowler reported a case of pyo-ureter after nephrectomy due to calculus in the ureter, and referred to Israel as having reported four cases of "empyema of the ureter" as a complication in 900 nephrectomies. Fowler's case was particularly interesting in that he observed the intermittent expulsion of thick pus from the ureteral meatus, thus establishing the fact that the ureter is capable of peristaltic contraction after nephrectomy. To these reported cases can be added another from the records of the last three years of the Mayo Clinic, in which the ureter required removal after nephrectomy.

Case A312821. Mrs. H. L., aged thirty-seven years, registered in the Mayo Clinic April 10, 1920. She gave a history of successful removal of a stone from the left kidney in 1915, with relief of symptoms for one year, when she had recurring attacks of renal colic which have persisted. A roentgenogram of the left renal area showed several shadows, and cystoscopic examination revealed a large infected hydronephrosis with a functionless kidney. Nephrectomy was performed April 26, 1920; an uneventful convalescence followed. On April 5, 1921, the patient returned, complaining that for the last two months there had been swelling and soreness in the region of the wound. A roentgenogram of the left kidney area revealed a shadow, 2 by 3 cm., opposite the third lumbar vertebra, and a lead catheter, introduced at cystoscopic examination, impinging against this shadow. There was no secretion from the left orifice. Diagnosis was made of stone in the left ureter, ureteritis, and abscess formation. At operation, April 11, 1921, the ureter was found distended with pus above a point completely blocked by a calculus, and there was marked peri-ureteral inflammation. About 8 cm. of the ureter, to a point below the obstruction, was removed. The patient was dismissed April 30 with a healed wound.

Surgical intervention for pyo-ureter after nephrectomy is rarely required, and usually the condition is due to stone in the ureter which prevents escape of the ureteral contents. The fact that the ureteral lumen is seldom so completely blocked by a calculus that the ureteral contents cannot gradually escape would account for the small number of cases reported. However, when the lower ureter is ligated with silk, as in resections of the bladder, and nephrectomy is required later, the possibility of pyo-ureter developing should be considered. This fact had been recognized by Hunt of the Mayo Clinic, who, while removing a kidney in which an acute septic condition had developed following ligation of the lower ureter with silk, provided for drainage of the ureter by insertion of a catheter into the ureter, bringing it out through the wound.

DISCUSSION

The experimental results obtained in the hydro-ureters and pyo-ureters depended entirely on whether or not the ureteral contents were evacuated. When drainage occurred the distended ureter became smaller, through collapse of the lumen and atrophy of the muscle coat, and peri-ureteral inflammation did not occur. When obstruction to drainage was present, the muscular hypertrophy remained and absorption of the ureteral contents seemed very limited if occurring at all. Infection of the ureteral contents, if not present at the time of nephrectomy, occurred later in some instances, and always spread through the ureteral wall to cause peri-ureteritis. Peri-ureteritis was present in every pyo-ureter in some degree varying from inflammatory adhesions to abscess formation. This would indicate that drainage of the ureteral contents should be provided for at the time nephrectomy is performed, if there is known or doubtful complete obstruction to such drainage into the bladder.

Atrophy of the muscular wall of the normal ureter after nephrectomy was a finding which was to be expected, as it simply represents the atrophy of disuse from the lack of any stimulus to ureteral contraction. Likewise, the gradual atrophy of the hypertrophic muscle, which had developed in the attempt to overcome the obstruction to the outflow of the ureteral contents, would seem a natural occurrence after the obstruction had been removed and the ureteral contents drained.

The greater muscular hypertrophy found at long periods after nephrectomy in the walls of the ureters with complete obstruction to the evacuation of their contents would indicate that such hypertrophy increased after nephrectomy. This would seem to be logical, providing the blood and possibly the nerve supply of the ureter were not interfered with, as the stimuli to ureteral peristalsis are present as long as the ureter is distended with fluid contents. Such must have been the condition in the case reported by Fowler; he observed, more than three years after nephrectomy, the intermittent forming of thick pus into the bladder. This case differed from the experimental cases in that there was some escape of the ureteral contents with each peristaltic wave, and brings up the question whether or not peristalsis persists when the lumen is distended and there is no escape of contents on contraction. Whether or not nephrectomy was performed would not affect the persistence of peristaltic contractions of the ureter after the point had been reached when the kidney ceased secreting urine, as the ureter is not dependent on the kidney for stimulus to contraction, except as it supplies the urine. The degree of muscular hypertrophy obtained in the complete obstruction experiments of Groups 2 and 3 would seem to indicate that peristalsis continues as long as a stimulus is supplied by ureteral contents, although this hypertrophy is not equal to that usually seen in experimental work, such as the transplantation of ureters, when there is partial obstruction to the lumen of the ureter. These findings would seem to warrant the conclusion that the hypertrophic hydro-ureter or pyo-ureter, with complete obstruction to evacuation of contents, will remain hypertrophic and atrophy will not occur in its muscular wall. This conclusion was substantiated by study of the walls of the ureter of the clinical case reported, as there was marked muscular hypertrophy.

The persistence of the mucous membrane in all of the experiments from the atrophic normal ureter to the large distended pyo-ureter was noteworthy. Except for the "ironing out" by distention of the normal mucosal folds the membrane was intact in every case, although in the infected cases it has permitted the migration of the infecting agent through to the submucosa and muscular wall.

CONCLUSIONS

1. In the normal ureter after nephrectomy no attempt is made toward obliteration of the lumen by disappearance or atrophy of the mucous membrane, but there is a noticeable atrophy of the muscular coat.

2. Hydronephrosis developed in every case following the production of complete obstruction of the ureter, the condition progressing to complete destruction of the substance of the kidney, unless the obstruction was removed.

3. The ureter, after complete obstruction, becomes a hydro-ureter by distention of the ureteral lumen with the retained urine. Hypertrophy of the muscular layers, chiefly of the circular, though also of the longitudinal layers, occurs.

4. In the hypertrophic hydro-ureter or pyo-ureter, with drainage of its contents after nephrectomy, the mucous membrane remains intact and the muscular coat gradually atrophies.

5. In the hypertrophic hydro-ureter or pyo-ureter with complete obstruction to drainage of the ureteral contents after nephrectomy, the mucous membrane remains intact and the muscular coats remain hypertrophic.

6. Absorption of the contents of a distended ureter is very limited if it occurs at all.

7. If infection is present in the contents of the ureter, it may spread through the wall and give rise to peri-ureteral infection and abscess formation.

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THE GRADUAL WITHDRAWAL OF RESIDUAL URINE FROM THE CHRONICALLY OVERDISTENDED BLADDER*

GORDON S. FOULDS

Patients with chronic retention of urine may be divided into two groups, those infected early, and those infected only after prolonged retention. In the latter group, particularly, retention due to prostatic hypertrophy is very insidious in its onset, and often remains undetected until some intercurrent infection takes place. With chronic overdistention of the bladder, particularly in the presence of infection, it is not uncommon to find the ureter and renal pelves dilated.

The patient who is suffering from retention of urine due to prostatic obstruction and who has been catheterized routinely is a better risk for operation on the lower urinary tract than the patient who does not have infection and has not been catheterized. It is recognized as a dangerous procedure suddenly and completely to empty a chronically overdistended bladder. With the sudden withdrawal of urine there is a corresponding sudden fall in intraversical pressure and release of tension in the bladder wall. This sudden decrease in pressure permits passive congestion, hemorrage, and edema of the mucous membrane of the bladder. The two methods advocated for emptying overdistended bladders are, (1) insertion of catheter, and intermittent drawing off of urine in small amounts, and (2) complete withdrawal of urine, and partial filling of the bladder with sterile boric acid solution. Neither of these methods avoids the danger of sudden decrease in intravesical tension. The method suggested by Van Zwalenberg for the gradual emptying of the bladder has been used in the Mayo Clinic since January, 1921.

METHOD OF APPLICATION

The patient is placed in a hospital and made comfortable in a warm bed. A soft rubber catheter is introduced with all aseptic precautions and fastened in place without permitting the escape of any urine. This procedure is possible except in occasional cases in which the catheter has to be passed on a metal guide. In such cases a minim loss of urine occurs, usually from 10 to 15 c.c. The catheter is then connected to a 6-foot rubber tube, connected at its distal end with one arm of a glass Y-tube. The other arm of the Y-tube is hooked over the edge of a receptacle hung at the foot of the bed. The clamp is then removed from the catheter and the receptacle for the urine is adjusted to a level at which the urine will just trickle over into it on deep inspiration. The tube is clamped when the patient is fed, bathed, or when any movement is to be undertaken which will disturb the relative level of the bladder and the outlet. An ordinary douche makes a good receptacle, since the accumulated urine may be removed from the outlet without disturbing its level. The receptacle is lowered 2.5 cm. each day until the bladder has emptied itself or until the level of the outlet is approximately that of the bladder. When this level is reached the bladder is usually almost, if not entirely, empty. Suprapubic drainage was established in one case in which urethral catheterization was impossible. This patient got along satisfactorily. (The case is reported in full in the original paper.)

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* Abstract of paper published in full in the Journal of Urology, 1921, v, 453–459. From the Section on Urology, Mayo Clinic.

TYPES OF CASES

Between January 1 and April 1, 1921, twenty patients have been treated at the Mayo Clinic by the method described. The average age of these patients was sixty-six; the oldest was seventy-seven, the youngest was fifty-five. Only two patients gave a history of previous cystitis; two had moderate amounts of pus in the urine. Fourteen patients had definite retention and overflow of from three months to one and a half years' duration. Seventeen had not been catheterized since definite retention developed. On physical examination all, with one exception, were found to have been in poor general condition. All had distention of the bladder sufficient to cause suprapubic tumor, the smallest extending 6 cm. above the pubis and the largest 2.5 cm. above the umbilicus. In six patients the bladder extended to the level of the umbilicus. Because of the nature of the withdrawal the exact amount of residual urine could not be determined. The phenolsulphonephthalein return was low in all cases. In only three cases was it 15 per cent and above, in three 10 per cent, and in thirteen cases it was nil, or a trace in two hours and fifteen minutes. The blood urea varied between 28 and 312 mg., the average being 81.4 mg. for each 100 c.c. of blood. The creatinin was estimated in eleven cases only. The highest creatinin estimation was 6 mg., the lowest 1.5 mg., and the average 2.4 mg. for each 100 c.c. of blood.

RESULTS

In twenty patients observed between January 1 and April 1, 1921, intravesical tension varied greatly; the highest was sufficient to raise a column of urine 27.5 cm. above the bladder level, the lowest was 10 cm., and the average was 14.8 cm. Most of the patients had a tension approximating the average. The rate at which the bladder emptied itself showed an equally wide range of variation and did not always bear a definite relationship to the tension. It took from two to eight days to empty the bladder; the average time was 4.3 days. The bladder which registered the highest tension, 27.5 cm., was emptied at the end of four days, when it still elevated a column of urine 17.5 cm. Another case, in which the bladder tension was 25 cm., required eight days to empty. In two cases there was urine in the bladder when the pressure was reduced to nil. In three cases hemorrhage, apparently due to trauma in the prostatic urethra, was appreciable; in each case it followed difficulty with the in-dwelling catheter, and ceased immediately the catheter was removed.

Eight patients had primary prostatectomy. Two had suprapubic drainage and subsequent prostatectomy. In one of these a two-stage operation was necessary because of the presence of a large vesical calculus. Four others had suprapubic drainage; one of these died after operation. He had progressed satisfactorily for four weeks previous to the time of operation, and death was in no way associated with the removal of the urine. One of these patients is awaiting secondary prostatectomy. One patient who had suprapubic drainage and four who had in-dwelling catheters had carcinoma of the prostate. These all progressed satisfactorily and have returned to their homes. One patient with benign hypertrophy of the prostate is at home for the summer and will return in the autumn for secondary prostatectomy. One patient with carcinoma and recent suprapubic drainage is still in the hospital.

PARTIAL SPONTANEOUS INVERSION OF A DIVERTICULUM OF THE BLADDER WITH DUMB-BELL STONE*

CHARLES R. B. CROMPTON

The extreme rarity of partial spontaneous inversion of a diverticulum of the bladder and also the coincident occurrence of a dumb-bell stone, presenting a clinical picture simulating carcinoma of the bladder with stone, rendering the differential diagnosis difficult, warrants this report. A search of the literature failed to reveal a report of a similar case.

REPORT OF CASE

Case A389878. Mr. J. K., aged sixty-two years, came to the Mayo Clinic April 25, 1922. For the past fifteen years the patient had had moderate frequency of urination. The first of four attacks of left renal colic occurred five years before, and on each occasion he had voided multiple stones. The onset was sudden, with typical radiation of excruciating pain from the left renal area posteriorly to the groin and penis. One year before he noticed burning in the urethra while voiding. This persisted for seven months when he noticed considerable difficulty. At times the stream would be suddenly shut off, and dribbling would continue until completion of the act. At other times the stream was normal in size. He complained of a dull, constant pain at the penoscrotal angle and in the perineal region. This was much exaggerated during and after voiding, and especially by sudden jarring while motoring or driving. During the last five months the frequency became more marked and he always had a sense of incomplete micturition.

Physical examination revealed a healthy appearing, obese man, weighing 231 pounds, which was slightly less than his usual weight. The blood pressure was 196 systolic and 126 diastolic. The teeth contained many fillings, and marked periapical granulomas were apparent in the roentgenograms. The tonsils were soft, spongy, and of the deeply crypted type, with marked infection. Both fundi showed marked retinal arteriosclerosis consecutive to hypertension. Rectal examination revealed the prostate to be firm but not enlarged. The vesicles were not palpable. The external genitalia were normal. On two successive days twelve-hour specimens of urine amounted to 300 and 500 c.c., with a specific gravity of 1.028 and 1.026 respectively. Both specimens were acid in reaction; there was a slight trace of sugar and moderate albumin on both heat and acetic acid and sulphosalicylic tests; the low power of the microscope revealed a moderate number of erythrocytes and many pus cells. Examination of the blood showed hemoglobin 70 per cent, otherwise normal. Blood urea was 40 mg. and urea nitrogen 18.6

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* Abstract of paper published in full in the Journal of Urology, 1923, ix, 283–288. From the Section of Urology, Mayo Clinic.

mg. for each 100 c.c. of blood. The combined intramuscular phenolsulphonephthalein test showed 30 per cent return, and a combined intravenous test 35 per cent return in two hours and fifteen minutes. A roentgenogram of the kidney, ureter, and bladder showed a shadow over the left bladder area; it was dumb-bell in shape, lay transversely across the pelvis, each extremity of the shadow measured about 2 cm. in diameter; the mesial portion was much more distinct than the lateral (Fig. 81). Cystoscopic examination revealed marked chronic diffuse cystitis with purulent urine in the bladder. In the left base of the bladder was a white stone about 2 cm. in diameter, apparently fixed to a tumor mass which elevated it from the bladder wall. The tumor had the appearance of a malignant papilloma of the solid type, and was about 3 by 4 cm. An attempt to dislodge the stone from the tumor with the beak of the cystoscope was unsuccessful. A specimen of the tumor obtained with the specimen-taker was found on pathologic examination to be "inflammatory tissue." The ureteral orifices were not seen, owing to the extreme degree of cystitis and to purulent bladder urine. On cystoscopy three days later litholapaxy was performed. At this time the tumor mass appeared clinically so malignant that the fragments of stone were not removed from the bladder, since resection of the tumor was thought advisable. A second specimen from the tumor was then obtained through the cystoscope with a specimen-taker. On microscopic examination this also proved to be inflammatory tissue.

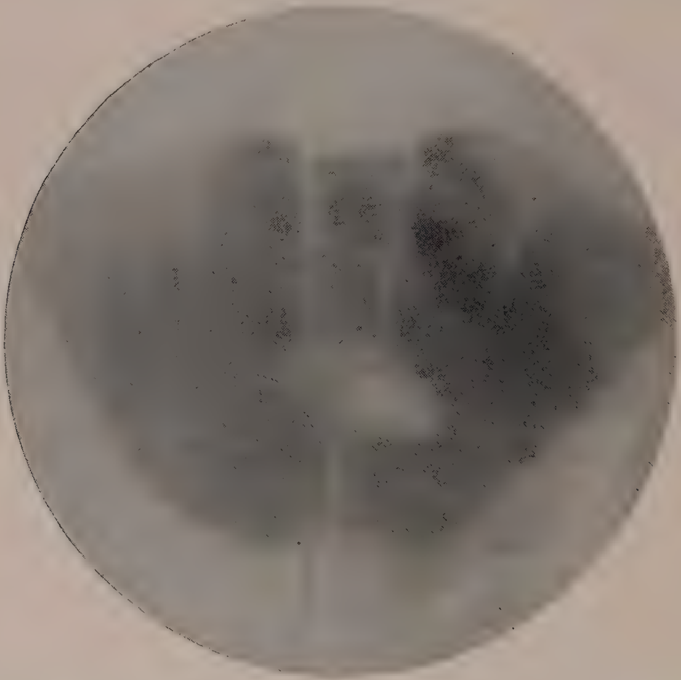

FIG. 81.—Roentgenogram of bladder area showing dumb-bell stone. Bladder portion distinct, diverticular portion just discernible.

Three days following the last cystoscopy a suprapubic midline incision was made and the bladder explored under ether anesthesia. The fragments of the bladder portion of the stone, crushed at litholapaxy, were found lying loose in the bladder. The tumor mass at the left base proved to be a small diverticulum almost completely inverted into the bladder cavity, and covered with extensive hypertrophic granulation tissue. A nodular, pyramidal shaped stone about 2.5 by 2.5 by 2 cm. was found lodged firmly in a sacculation at the apex of the inverted diverticulum. Several small stones were also found impacted between what had been the orifice of the diverticulum and its inverted wall. The inverted diverticulum, which proved to be about 3 cm. in diameter and the same length, was dissected from the bladder wall, but on account of its friability could not be preserved intact. The cut edges of the neck of the sac were then cauterized with the actual cautery. Marked chronic cystitis was present. No intravesical enlargement of the prostate could be demonstrated. The pathologic report of the tumor mass was again "inflammatory tissue" with an ulcer about 2.5 by 2 cm. which had, apparently, contained the diverticular portion of the stone. On the bladder surface of the diverticular stone was an area of recent fracture from which the bladder portion of the stone had been broken off at litholapaxy; this showed it to be a dumb-bell stone (Fig. 82). The patient made an uneventful recovery with complete relief of symptoms.

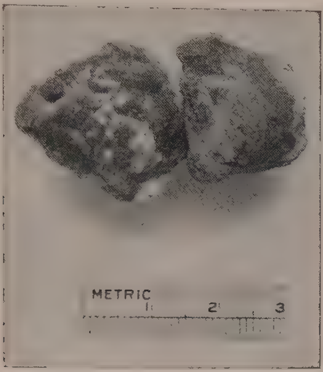

Fig. 82.—Postoperative specimen of stone with fragments fitted in their original positions.

DISCUSSION

Previous to the observation of this case twenty-eight cases of coincident bladder stone and diverticulum had been reported from the Mayo Clinic. Five other cases of dumb-bell stone of the bladder are on record in the literature; one was reported by Young, one by Davis, one by Martin, and two by Crenshaw and Crompton. Including the case reported herein, four have occurred at the Mayo Clinic.

The history of repeated renal colics with the passage of stones points to the kidney as the source of the stones in this case. Possibly the stones passed into the bladder, were forced into the diverticulum, and produced the marked secondary inflammatory changes in the sac. A diverticular stone may have gradually grown and protruded into the bladder, acting as a nucleus for the formation of the bladder portion of a dumb-bell stone. It is difficult to determine how almost complete inversion of the diverticulum into the bladder occurred. Possibly in an endeavor on the part of the bladder to expel the bladder portion of the dumb-bell stone the sac was inverted, impacting the smaller diverticular stones in its edge. Another factor in the production of bladder and diverticular stones is the etiologic relationship between stone formation and diverticulum of the bladder. This case also demonstrates that occasionally a benign tumor of the bladder or an inverted diverticulum may appear, clinically, very malignant, which emphasizes the necessity for microscopic examination, so that the degree of malignancy may be estimated in all cases of bladder tumor. Broders has pointed out that the degree of malignancy materially alters the mode of treatment and ultimate prognosis of the case.

FOCAL INFECTIONS IN RELATION TO SUBMUCOUS ULCER OF THE BLADDER AND TO CYSTITIS*

JOHN G. MEISSER AND HERMON C. BUMPUS, JR.

Infection of the urinary bladder not secondary to infection of the kidney or perivesical disease often is attributed to a pyelonephritis which has subsided. The kidneys, however, do not exhibit evidence of former disease, the function and pyelograms being normal and the urine sterile. If this explanation were correct, it would be difficult to understand why the kidneys, the more vulnerable organs, should recover and the bladder remain involved. If it is assumed that such cases of cystitis are of focal origin, instead of being invariably the result of an adjacent infection, many aspects of the disease can be explained.

Under certain conditions the infecting organism may cause generalized cystitis or, if the inflammation becomes localized in one area of the bladder, necrosis of the mucosa will result in a simple ulcer of the bladder. The organism may lodge deeper in the wall of the bladder. In such an event the pathologic process will occur entirely below the mucosa and that rare type of ulcer first described by Hunner results. We refer to this condition as "submucous ulcer," which seems a concise and descriptive term, differentiating clearly the condition from simple ulcer of the bladder in which the destruction of the mucosa is extensive.

The changes in the tissues in submucous ulcers indicate a blood-borne infection. The blood vessels are prominent; polymorphonuclear leukocytes and lymphocytes and extravasated erythrocytes are found not only within the lumen but also infiltrating the vessel walls and perivesical tissue. Since these perivesical changes with the cellular infiltration and edema are most marked in the outer coats of the bladder, it would seem that the infection is not carried by the urine. The urine is usually sterile, which is a further indication that the etiology of the condition must be sought outside the urinary tract.

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* Abridgement of paper published in full in the Journal of Urology, 1921, vi, 285–298. From the Division of Experimental Bacteriology, Mayo Foundation, and the Section on Urology, Mayo Clinic.

Often in simple ulcers of the bladder and idiopathic cystitis urine is found to be infected with the colon bacillus. This organism has, therefore, been considered the causative factor. By recent experimental investigation, however, we have shown that pyelonephritis may often be due to focal infections harboring streptococci which have selective affinity for the urinary tract, and that the colon bacillus, which is commonly found and generally believed to be the cause, is of secondary importance.

If we assume that vesical infections are of hematogenous origin, it is natural to attribute the source of such infection to oral sepsis, which often is the cause of other diseases. Hunner has suggested this with regard to submucous ulcers, but regrets that clinical evidence is not sufficient to prove it. The work of Rosenow on the elective localization of streptococci also strongly suggests this theory as an explanation.

We have reviewed carefully the histories of fifteen patients with submucous ulcers operated on at the Mayo Clinic. Seven of these had had tonsillitis, three had had tonsillectomies; five had had grippe; three had had scarlet fever, and one had had rheumatism. On careful dental examinations eleven patients showed evidences of periapical infection. This is an unusually large incidence of infection in a group of fifteen patients, and is significant, especially when it is borne in mind that all of these infections were associated with streptococci.

Because the findings in our cases were so indicative of focal origin of vesical infections, all patients with such infections were carefully examined for evidence of oral sepsis. The examination of their teeth included not only roentgenograms to demonstrate the presence of apical abscesses and devitalized teeth but also careful examination of all teeth by means of the pulp tester in order to ascertain their viability. This was done because in making routine cultures of extracted teeth we have found that at the apices of pulpless teeth pure cultures of green-producing streptococci may be isolated even when the roentgenograms do not show evidence of periapical infection. The exclusion of the teeth, therefore, as a possible focus of infection simply because apical abscesses are not demonstrable by the roentgen ray we believe to be an error. The same may be said of the tonsils; the fact that they are not enlarged and that pus cannot be expressed does not exclude them as possible foci.

In cultures obtained from the extracted teeth green-producing streptococci were always isolated. From the tonsils more varied flora were obtained, which, however, always included green-producing streptococci.

The technic employed in isolating bacteria and in injecting animals was that described in our report on pyelonephritis.

In the series of the six patients reported in this investigation five gave histories of previous tonsillitis; in three it had been sufficiently severe to require tonsillectomy. In one case an infected tonsillar remnant furnished the cultures for our experimental work. Five of the six patients had dental sepsis.

Four patients had had symptoms pathognomonic of submucous ulcer of the bladder; the presence of the ulcers was confirmed by cystoscopic examination. The urinalysis in each case was negative for a few erythrocytes and an occasional leukocyte. One of the remaining two patients had diffuse cystitis of unknown origin, the other a simple ulcer of the bladder. In both the urine from the bladder was highly infected.

REPORT OF CASE

Case A338027. Miss L. C., aged forty-five years, registered in the Clinic October 18, 1920. She had had frequent attacks of right sided abdominal pain, which often had been diagnosed cholecystitis. She had also had many attacks of tonsillitis, as a result of which her tonsils had been removed some years before. The present trouble had begun five years before with pain in the region of the bladder, which occurred on the least distention, was accompanied by a frequent desire to void, and was followed by terminal tenesmus and pain. She had found it necessary since the onset of the trouble to void from two to eight times at night, and hourly during the day, but she believed that a normal amount was voided in twenty-four hours. She had not seen blood and had not had incontinence. When moving around she often experienced a sharp stabbing pain in the region of the bladder. Many urinalyses had been made and reported to be negative.

The patient's general examination in the Clinic, including roentgenographic examination of the urinary tract and urinalysis, was negative. Cystoscopic examination disclosed two areas in the dome of the bladder, each approximately 0.5 by 1 cm., with small blanched centers from which multiple engorged vessels radiated in an area of increased inflammation and edema. These spots were excessively tender to palpation with a ureteral catheter and produced the stabbing pain of which she complained.

Roentgenograms of the teeth revealed evidence of periapical infection at the roots of six. These were removed surgically, two at a time, at intervals of eight and fourteen days, and pure cultures of green-producing streptotocci were obtained from each. Following extraction of the teeth the patient had a marked exacerbation of urinary symptoms and a recurrence of the former cholecystitis, with considerable pain below the right costal margin.

Primary cultures from the infected teeth were injected into six rabbits. Five developed lesions in the urinary tract; two had marked edema and swelling of the mucous membrane of the bladder, with multiple submucosal hemorrhages, and the gallbladders were markedly thickened, red, and edematous. In three animals relatively slight lesions, other than those in the urinary tract or gallbladder, were found. Two had lesions in the endocardium; one also had slight joint involvement, and one had a few punctate hemorrhages in the stomach. The streptococci were recovered in pure culture from the lesions in the kidneys and from the urine in all but the negative rabbit, and from the bile of the rabbits that had lesions in the gallbladder. The streptococci recovered from the lesions in the urinary tract of these rabbits were injected into two normal rabbits. Both developed lesions in the urinary tract only. The streptococci were again recovered from the lesions in pure culture.

During the reaction which followed the removal of the infected teeth many green-producing streptococci and gram-negative bacilli were found in a catheterized specimen of the patient's urine. Two rabbits were injected with the cultures; one developed marked lesions in the urinary bladder and in the gallbladder (Figs. 83 and 84), and both rabbits had lesions in the kidneys. Streptococci and gram-negative bacilli were isolated in cultures made from the lesions.

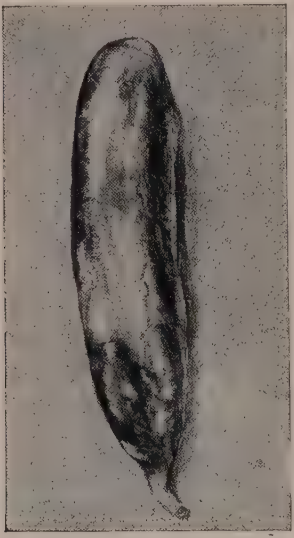

FIG 83.

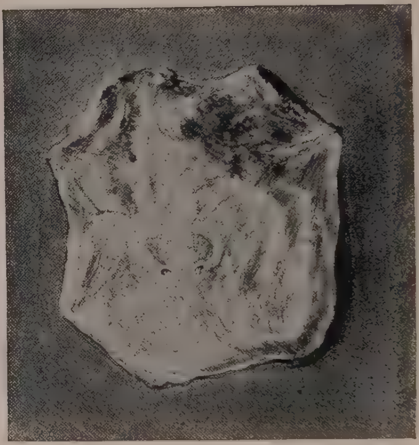

FIG. 84.

FIGS. 83 and 84 (Case A338027).—Rabbit's urinary bladder and gallbladder showing edema and hemorrhage following an injection of a culture obtained from patient's urine.

Three of the ten animals used in this study had marked lesions in the urinary bladder and in the gallbladder, and nine had lesions in the urinary tract. The urine from all the animals was examined prior to the injection and was negative. At necropsy six of the rabbits had urine in the bladder, in five of which pus cells, erythrocytes, and albumin were found.

DISCUSSION

Thirty-three animals were injected with cultures from the six patients; nineteen with primary cultures from the teeth or tonsils, five with cultures from lesions in animals injected with primary cultures, and nine with cultures from patients' urine. Of the series of nineteen animals injected with primary cultures from the teeth or tonsils, sixteen had lesions of the urinary tract, thirteen of which were in the urinary bladder. Two had lesions in the gallbladder, four had small hemorrhages in the stomach, five had hemorrhages in the endocarcium, and one had slight joint involvement.

On second animal passage five animals were injected with streptococci isolated from lesions in the kidneys and from the urine of rabbits injected with the primary culture. Four of the five had lesions in the medulla of the kidney. There were no extra-urinary lesions.

Nine animals were injected with cultures from the patients' urine. Five of the nine were injected with mixed cultures of colon bacilli and streptococci. Three had lesions in the kidney, one had lesions in the urinary bladder, one in the gallbladder, and two in the joints. Two were injected with a culture containing streptococci and staphylococci; both developed lesions in the kidneys. Two were injected with pure cultures of colon bacilli; both were negative at necropsy. In these nine animals, as in those used on second animal passage, the lesions occurred mainly in the kidneys; very few lesions occurred outside the urinary tract.

It seems certain that the marked affinity of these strains for the urinary tract is not accidental because only ten of 239 animals under the same conditions developed lesions in the urinary tract following injection with streptococci from infected teeth and tonsils of patients having diseases other than urinary infection.

Specimens of catheterized urine from all rabbits were normal before injection; after injection a small amount of albumin, with relatively few erythrocytes and a number of leukocytes and epithelial cells, was found.

The bladders of the rabbits were usually contracted, the walls edematous, and the vessels markedly injected. Scattered throughout the walls were numerous hemorrhagic lesions involving the submucous tissue and the mucous membrane. These varied in size from small punctate areas to lesions that were from 3 to 4 mm. in diameter. There were many polymorphonuclear and mononuclear leukocytes in the submucosa and around the dilated blood vessels. Sections stained by the Gram-Weigert method revealed many gram-positive diplococci in various stages of digestion.

Two of the patients with submucous ulcers of the urinary bladder were operated on, and examination of the specimens made. The microscopic picture was about the same in both. There was a loss of epithelium in the ulcer-bearing area. In the submucosa where the most

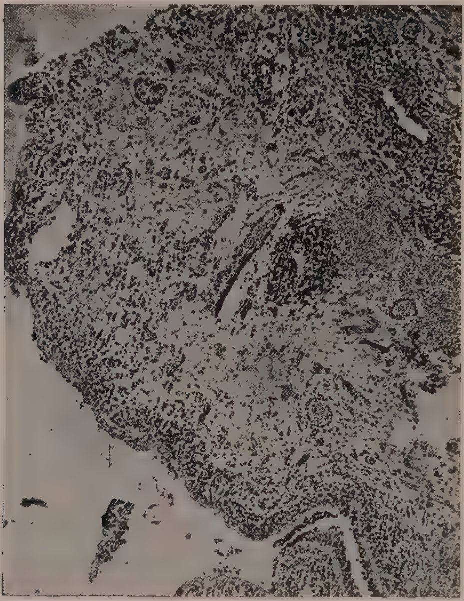

FIG. 85.—Section of the submucous ulcer. Areas of round-cell infiltration and loss of epithelium. Hematoxylin and eosin. (×50.)

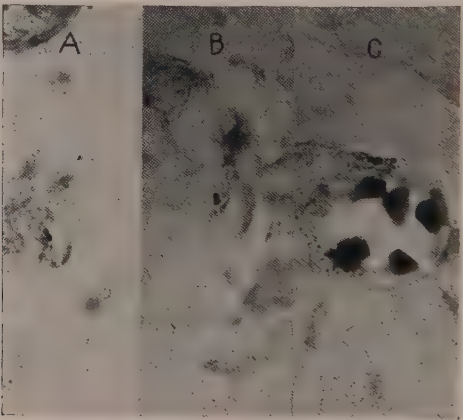

FIG. 86.—Diplococci in perivascular areas and other areas of round-cell infiltration. Gram-Weigert. (×1000.)

extensive changes took place were many large and small areas of round-cell infiltration (Fig. 85), as well as many newly formed blood vessels. The muscular coats were somewhat edematous, but with very little round-cell infiltration. The peritoneal coat was slightly thickened. A prolonged search of carefully stained sections from the ulcers demonstrated undoubted diplococci within the lesions (Fig. 86).

We believe that finding these streptococci in the excised ulcers and our experimental work demonstrates that submucous ulcers of the bladder and other infections of the urinary bladder may be due to focal infections harboring streptococci which have a selective affinity for the urinary tract.

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THE LATE RESULTS OF OPERATIONS FOR THE CURE OF EXSTROPHY OF THE BLADDER*

ARTHUR R. KNAUF

Early methods of treatment of exstrophy of the bladder consisted in attempts to remedy the condition by means of plastic operations. Many ingenious operations were devised, such as closing of the bladder with skin flaps or suturing the edges of the bladder mucosa together. In general these plastic operations were distinct failures. The mortality of the operations was high. Continence of urine was rarely secured and in most cases repeated attempts at closure were necessary.

In order to obtain continence surgeons early tried diverting the urine to the intestine. Various methods of communication between the ureter and intestines were attempted. Many of the first operations had a high mortality due to peritonitis and ascending pyelonephritis.

Maydl, in 1892, transplanted an oral portion of the trigone containing the ureters into the rectum. The ureteral openings were kept intact by this method, and it was hoped that this would avoid the ascending of infection which caused such a high mortality in this type of operation. For many years the Maydl operation with several modifications was the operation of choice; the mortality was high (28.7 per cent) in eighty cases collected by Buchanan. The majority of the deaths were due to pyelonephritis and peritonitis. Rectal irritation in these cases is rare. Control, though acquired gradually, has usually been good following this procedure. As a result of the high mortality in these cases attempts were made to develop a technic which would diminish the risk of peritonitis and pyelonephritis.

Oblique implantations of the divided ureters were made by Martin in 1899. Stiles implanted the divided ureters, using a modification of the Witzel gastrostomy method with some success. In an effort to simulate the entrance of the bile and pancreatic ducts into the intestine Coffey, in 1911, developed a technic to diminish the ascending infections which had been the most common cause of the high mortality of the previous operations. This operation, with changes as suggested by C. H. Mayo, has been adopted at the Mayo Clinic. The ureter is divided approximately one inch from the bladder. On the right side an incision one and one-quarter inches in length is made in a longitudinal direction through the serous and muscular coats of the rectosigmoid. The mucosa is left intact except at the lower end, where a puncture is made large enough for the passage of the ureter. The ureter is then inserted for a short distance into the lumen of the intestine. It is fixed by interrupted sutures passing through serosa, muscularis, and wall of the ureter. Some weeks later the left ureter is implanted in a similar manner into the sigmoid. By this method the ureter is made to traverse one and one-quarter inches of the wall of the intestine and any pressure from within will tend to close the lumen of the ureter.

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota, in partial fulfilment of the requirements for the degree of Master of Science in Urology, 1922. From the Section on Urology, Mayo Clinic.

Since the adoption of this method thirty-three patients have been operated on for exstrophy of the bladder at the Mayo Clinic. The operation was performed in three stages; the right ureter was transplanted first. After a lapse of from ten days to two weeks the left ureter was transferred, and later the bladder mucosa was excised. Twenty-three patients are well from nine months to twelve years after operation. None of them complain of symptoms which could be attributed to renal insufficiency or pyelonephritis. Seventeen have survived the operation for three or more years, and six for five years. One patient is married and has successfully passed through a pregnancy. Urinary control has been very satisfactory in all instances and these patients have been transformed into useful and self-sustaining citizens. An opportunity was afforded to reëxamine five of these patients at different intervals following operation.

REPORT OF CASES

Case 1 (A228976). Mr. H. S., aged nineteen years, came to the Clinic April 20, 1918, complaining of urinary incontinence. He had lost 25 pounds in two months. Physical examination revealed exstrophy of the bladder. There was also a palpable mass in the left upper quadrant of the abdomen. A diagnosis of left pyonephrosis was confirmed at operation and a left nephrectomy was performed. Later the right ureter, though markedly dilated, was transplanted into the colon by the Coffey method. From this procedure the patient recovered without incident. Two years later he felt perfectly well. He had been able to work almost constantly since leaving the hospital. General examination was practically negative.

Case 2 (A259298). Miss E. B., aged nineteen years, was examined at the Clinic February 11, 1919, because of exstrophy of the bladder. Examination revealed complete exstrophy of the bladder. At operation a large left hydro-ureter and hydronephrosis were found. The right ureter, which was normal in size, was transplanted into the rectosigmoid. Eighteen months later the patient was reëxamined. She had had no symptoms of renal infection; urinary control was fairly good. Urination occurred six times a day and three times at night. Blood examination, including tests for urea nitrogen, creatinin, and uric acid, were normal.

Case 3 (A251343). Mr. C. S., aged twenty-three years, came to the Clinic November, 1918, on account of complete exstrophy of the bladder. Both kidneys and ureters were apparently normal. The right ureter was transplanted into the sigmoid November 22, and the left December 2. Twenty-two months later he returned to the Clinic feeling perfectly well. Urinary control was perfect, and the physical examination proved him to be in excellent condition.

Case 4 (A238459). Mr. W. R., aged seventeen years, came to the Clinic in July, 1918, on account of exstrophy of the bladder. Operation had been performed nine times without relief. Both ureters were transplanted into the sigmoid at separate operations. On reëxamination, two years later, his health was good. There was no evidence of urinary infection and proctoscopic examination was negative. A letter three years after his original operation stated that he was in good health and had successfully passed through an operation for appendicitis.

Case 5 (A93590). Miss M. D., aged twenty years, came to the Clinic in October, 1913, on account of complete exstrophy of the bladder. Both ureteral orifices were visible and functioning normally. The ureters were implanted into the sigmoid in separate operations and the bladder was excised later. For seven years after her operation she has been a nurse and was in good health in 1922. Her sphincter control is perfect. There have been no signs or symptoms of pyelonephritis, and at the present time her blood chemistry is normal.

FACTORS INFLUENCING MORTALITY IN TUMORS OF THE BLADDER*

ALBERT J. SCHOLL

The mortality following the removal of tumors of the bladder depends primarily on whether the growth is benign or malignant, and if malignant, on the degree of malignancy. The location and size of the tumor are next in importance; if it is in an accessible region it may be removed completely, and a permanent cure may result. The age and resistance of the patient are also determining factors; young adults stand the shock of operation well, but they may have extensive growths of a high degree of malignancy.

Two hundred sixty-two cases of tumor of the bladder were studied in an endeavor to ascertain the relationship of mortality to the location of the tumor, the type of malignancy, and the age of the patient.

As might be expected, tumors of the base of the bladder, especially those involving the trigone, show a relatively high mortality. This is undoubtedly due not only to the technical difficulty of the operation, but to the impossibility of completely eradicating malignant tumors in this region. Ureteral involvement does not appreciably increase either the early or late mortality. There is practically no difference in the outcome when the ureter is involved; whether it is transplanted or merely ligated, the mortality is the same. Undoubtedly in some cases the additional time required for the more difficult transplantation overbalances any gain resulting from preserved renal function (Table 1).

Tumors of the dome, on account of the accessibility of the growth and the freedom from involvement of neighboring structures, give a low immediate mortality. The late results are not so satisfactory, probably owing to the high grade of malignancy of the low, flat, infiltrating tumors located in this region. In the later stages the tumors sometimes extend to the lateral wall, thus accounting for the high mor-

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* Abridgement of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Urology, 1922. From the Section on Urology, Mayo Clinic.

TABLE 1

Location of Growth and Postoperative Results

Location.	Patients.	Patients living.	Postoperative life, years.	Dead.	Dead, per cent.	Average duration of life, months.	Operative patients.	Mortality, per cent.
Lateral wall	58	33	3.5	25	43.1	9.0	7	12.7
Dome	7	4	2.7	3	42.8	2.7	1	14.2
Dome and lateral wall	13	4	2.5	9	69.2	9.0	3	23.0
Base and lateral wall	37	26	2.8	11	29.7	6.0	3	8.1
Base and lateral wall involving ureter	46	16	3.7	30	65.2	8.0	7	15.2
Base	14	5	3.5	9	64.2	6.0	3	21.3
Base and anterior wall involving sphincter	11	6	3.0	5	45.4	3.0	2	18.1
Anterior wall	5	3	3.5	2	40.0	11.0	0	
Diffuse	14	3	2.3	11	78.5	5.0	3	21.4
	205	100		105			29	

tality in cases in which the growths are in the upper bladder wall. Of five extensive adenocarcinomas of this series four were in the apex; the fifth was in an exstrophied bladder. The anterior wall was rarely involved alone. If this occurs, the tumors are generally large.

MORTALITY ACCORDING TO AGE

Owing to the type of malignancy, the mortality in cases of tumors in infants and young children is exceedingly high. The majority of growths in early life are of the connective tissue variety, often showing sarcomatous changes. They grow rapidly and may become very large and cause obstruction. There is a marked tendency to recurrence after removal (Table 2).

TABLE 2

Relation of Age to Mortality in the Operable Cases

Age.	Patients.	Patients living.	Postoperative life, years.	Dead.	Dead, per cent.	Average duration of life, years	Operative patients.	Mortality, per cent.
20 to 30	6	4	1.7	2	33.0	1.0		
31 to 40	12	9	2.0	7	58.3	1.7		
41 to 50	42	24	4.0	18	42.8	4.2	5	11.8
51 to 60	72	32	3.6	40	55.5	1.0	9	12.0
61 to 70	66	30	2.4	36	54.5	0.5	15	22.8
71 to 80	14	5	2.0	9	64.3	0.8	2	14.3
Total	216	104	3.2	112	51.8	0.9	31	14.5

Because of the general good health of most of the patients in early adult life the operative mortality is relatively low. Contrary to the usual opinion that there is a high percentage of early recurrence and a high death rate in young persons operated on for tumors of the bladder, these data seem to show that the patients have a comparatively good chance to recover ultimately. The optimal period of life for this condition, as shown by this series, is between forty and fifty years. At this time the lymphatics are not so active and the person still has the robust health and resistance of middle age.

Tumors of the bladder in persons more than seventy years of age are generally malignant papillomas and are often small. The operative mortality in such cases is low. In extreme old age many patients die of other complaints, consequently the late results seem to be unfavorable.

MORTALITY

There were 168 epithelial tumors. Seventy-four were papillomas, of which seventy-one were malignant; ninety-one were either solid epitheliomas or carcinomas. The malignant papillomas and epitheliomas are readily distinguished grossly and this division is of distinct prognostic importance. Eighty per cent of the patients who die with either type of malignancy, die in the first year. Forty-five (64 per cent) of the patients with malignant papillomas were alive and well on an average of twenty-seven months after operation. In contrast to this only twenty-seven (29 per cent) of the patients with epitheliomas or solid tumors were alive an average of thirty-seven months after operation. The total number of patients living three years after operation is four times as great in the malignant papilloma group as in the solid tumor group.

PATHOLOGIC CONDITION

Squamous-cell tumors.—Squamous-cell carcinomas are distinct individual types of epithelial growths. Their onset is insidious, their growth is rapid, and they cause few distinctive symptoms. They probably develop from metaplastic bladder mucosa which has undergone epidermization as a result of irritation from infection or formation of stones. The tissue in most cases is firm and friable. The growths involve the wall of the bladder extensively, and are flat and often ulcerated; the lateral margins slope out toward the mucosa, sinking deep into the underlying tissues. Sometimes patches of leukoplakia, giving a clue to the origin of the malignancy, are found in the region of the tumor. Squamous-cell growths are most often found in early middle life and are not uncommonly preceded by evidence of long standing cystitis. Compared with other epithelial tumors, these growths occur relatively

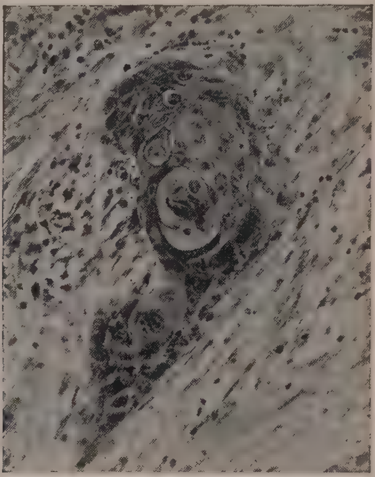

Fig. 87 (Case A203917).—Isolated area of squamous-cell carcinoma found in muscular wall of bladder. (×200.)

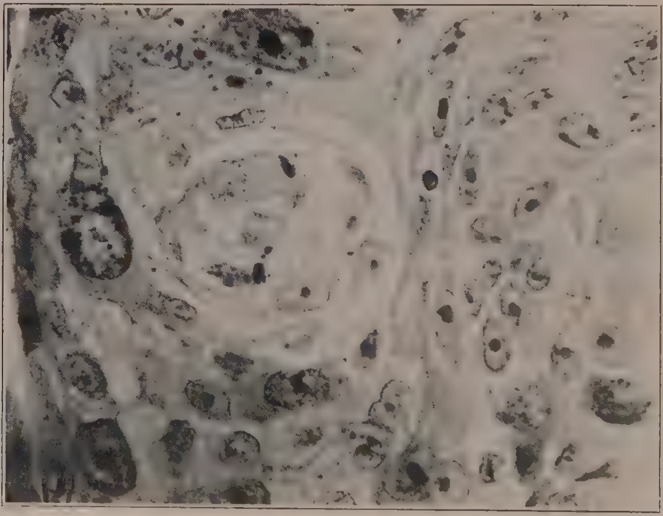

Fig. 88 (Case A203917).—Atypical mitotic figures. Irregularity in size and staining quality of cells in an epithelioma of the bladder. (×500.)

more often in females. While metastasis is not uncommon, death in most instances is due to the obstruction and infection resulting from the local lesion. The histologic examination generally reveals marked cellular activity. The cells are large and irregular, they stain deeply and contain many atypical mitotic figures. In some tumors extreme hyalinization and pearly body formation are found, indicating a long standing, possibly premalignant stage. These tumors are the most malignant of the epithelial growths of the bladder. The tumor projects rapidly and extensively into the deeper tissues; even in the region of the advancing border, finger-like extensions are seen separating the underlying muscle bundles.

In this series there were six squamous-cell carcinomas; three were seen in the operable stage and are included in the classification of solid carcinomas. The average preoperative duration of symptoms in the three patients was only three months; one patient had a recurrence four months after operation, and died eight months later; one died six months after operation, and the third patient is living and well nine years after operation. The conditions of the other three patients were inoperable; they were seen on an average of twelve months after the onset of symptoms referable to the growth in the bladder (Figs. 87 and 88).

Adenocarcinoma.—Glandular types of malignancy are observed occasionally. In all probability these growths arise from the glands of Limbeck and Brunn, or on the basis of cystitis cystica. They are generally large, often ulcerated, and involve the bladder wall only moderately. They have about the same degree of malignancy as malignant papillomas. There were five cases of adenocarcinoma in this series (Figs. 89 and 90). One patient had an inoperable recurrence two years after a resection of the growth. Three patients are living and well on an average of two years after operation. The fifth patient was a girl of twenty-one who had adenocarcinoma of an exstrophied bladder. The ureters in this case were transplanted to the large bowel and the bladder and malignant area were completely removed. Two years later the patient died from recurrence. The cases of malignancy in exstrophy of the bladder form an interesting group. As a result of constant irritation and trauma, an extensive glandular covering, a hyperplasia of the glands of the mucosa, develops. The glandular structures often show characteristics approximating malignancy. In a series of exstrophied bladders studied grossly and microscopically there was a gradual

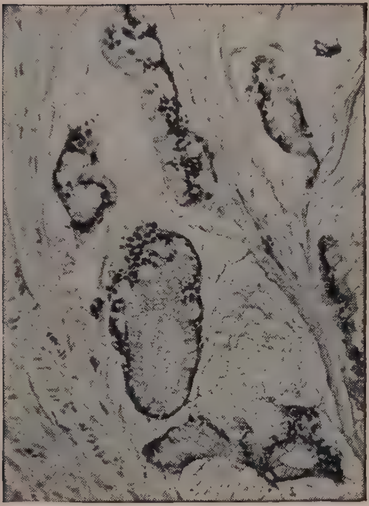

FIG. 89 (Case A346328).—Colloid adenocarcinoma of the bladder. (×100.)

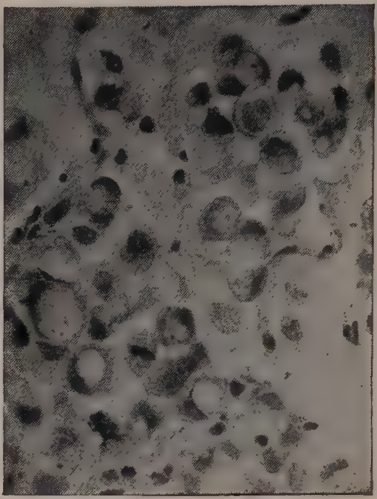

FIG. 90 (Case A270742).—Colloid carcinoma with mitotic figures and large vacuolated cells. (×500.)

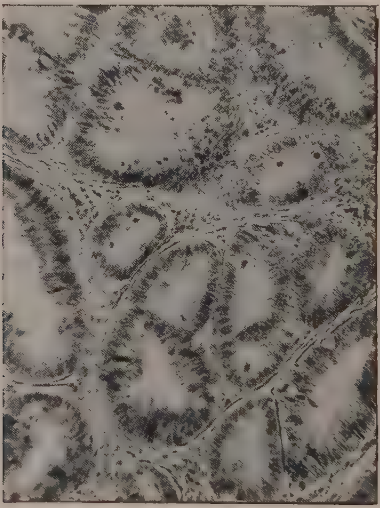

FIG. 91 (Case A190148).—Adenocarcinoma from an exstrophied bladder. (×200.)

increase in the extent of the hyperplasia and the approximation of malignancy that varied to a certain extent directly with the age of the patient. In the cases in which malignancy develops the tumor is always an adenocarcinoma, a type which would develop directly from hyperplastic adenomatous tissue (Fig. 91).

Angioma.—Angiomas are rarely found in the bladder. They may be small, and their only symptom a persistent profuse hematuria; or they may be extensive, penetrating into the perivesical tissues, and simulating growths of other pelvic organs. In most cases they are composed of anastomosing dilated cysts filled with blood; rarely they occur as branching masses of apparently recently formed blood vessels, supported by a fibromyxomatous stroma. There were three cases of angioma in this series. Only one was operable. This patient, a girl aged twenty years, is living and well, with a normally functioning bladder, six years after the removal of an extremely large tumor with one-half of the bladder wall.

Myoma.—Myomas of the bladder are similar to myomas of the uterus. They are rarely a pure type; they are generally fibrous and benign, although they sometimes show malignant characteristics. They are submucous, interstitial, or peripheral in type. Profuse hematuria is a common symptom and is occasionally combined with a palpable obstructing tumor. They are about equally divided between the sexes and have no predilection for any special period of life, although relatively they are found more often in infancy and childhood. Six of forty-one cases reported by Concetti in children were myomas. These growths are generally located on the trigone or posterior wall of the bladder, and are often pedunculated. Blum reports a case of torsion of a myomatous pedicle. The myomas are generally covered with a thinned-out mucosa which often presents an ulcerated, easily bleeding surface. Because of this covering the tumors are not infrequently considered extravesical when examined cystoscopically. The surface of the tumor is often marked with a network of dilated veins. Myomas, in most cases, are relatively large. Polaillon reports a case in which the tumor, removed by laparotomy, weighed 3 kg. Kouznetski described an enormous fibromyoma weighing more than 9 kg. and with a circumference of 68 cm. This tumor, which was pedunculated, grew from the posterior and superior wall of the bladder; it extended to the umbilicus and markedly compressed the uterus and rectum. The growth was resected through a median abdominal incision.

There was one case of fibromyoma in this series. The patient (Case A62897), a man aged fifty years, had had painless hematuria for years. At operation a hard, smooth tumor 9 cm. in diameter was enucleated from its attachment to the anterior wall of the bladder just above the sphincter of the urethra. Eight years later the patient was living and well.

Myxoma.—Generally myxomatous tumors are found in infants and children, rarely in adults. They are usually small, although they vary greatly in size, at times almost filling the bladder. They are often multiple and pedunculated, arising from the mucosa in the base of the bladder or from the region of the internal meatus. They are soft, gelatinous, and practically always covered with bladder mucosa, greatly resembling nasal polpys in their structure, though they are firmer and more fibrous. Because of their location and pedunculated attachments the tumors often cause obstruction; they grow very rapidly and if not completely removed have a marked tendency to recur.

There were two cases of myxoma in this series. One (Case A229590) was a child, aged two years, who had been having urinary difficulty and retention for several months; a soft mass protruded from the urethra. At operation a large, lobulated, soft, friable tumor 8 cm. in diameter was found. The tumor was completely removed, but the patient died two months later. The second child (Case A323590), aged sixteen months, had had gradually increasing dysuria for four months with recent hematuria. At operation an inoperable tumor was found involving the right wall and urethral sphincter. Nine days later the child died. At necropsy the tumor was found to be pedunculated; in its greatest diameter it measured 6 cm. The patient also had an extensive generalized miliary tuberculosis.

Sarcoma.—Sarcomas, like other connective tissue tumors of the bladder, occur earlier in life than epithelial tumors. They are exceptionally rare and extremely malignant. They are soft, friable, and sometimes villous. In the early stages they are small, single, and well localized. Although occasionally they are pedunculated, they usually are sessile, with broad bases. Ulceration is rare; metastasis and infiltration and extension to neighboring organs are common.

In forty-six necropsied cases collected by Munwes (1910) metastasis was found in 50 per cent. Geraghty found only two sarcomas in 180 cases.

Only one case (Case A3111) of sarcoma was found in the series of 262 cases. The patient was a woman, aged thirty-nine years, who had been troubled with frequency and hematuria for eighteen months. On examination a large, hard mass was felt in the area of the bladder. An inoperable tumor was found in the dome of the bladder. The growth extended into the suprapubic tissues. An excised specimen showed the condition to be sarcoma. The patient readily recovered from the exploratory operation, but died two years later.

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PREOPERATIVE TREATMENT OF MALIGNANT TUMORS OF THE BLADDER BY RADIUM*

ALBERT J. SCHOLL AND WILLIAM F. BRAASCH

Certain types of tumors of the bladder respond readily to excision, others offer an extremely poor prognosis. Owing to the difficulty of completely eradicating the tumor and its frequent cellular transplants, recurrence is early and extensive. This is particularly true of the solid, meaty epitheliomas which commonly occur in the base of the bladder. Small infiltrating wedges of actively malignant cells which project down through the muscle bundles are often cut across when a portion of the bladder is excised. The undisturbed clumps of cells which remain in the normal tissue act as foci, spread rapidly and extensively, and often soon attain an inoperable size.

Epithelial tumors of the bladder rarely metastasize; patients who die from malignancy of the bladder usually succumb because of the local condition. Any procedure that would aid in effectually eliminating the local condition would in many cases cure the patient.

Recently the flat infiltrating tumors have been treated with radium emanations prior to operation. Small amounts of radium are used with the idea not of completely destroying the growth but of diminishing the capacity of the cell for proliferation. This is done in an attempt to inhibit early recurrences from segments not removed and to prevent reimplantation of cells freed during the excision of the tumor.

Under sacral anesthesia the direct cystoscope is passed, the distal opening of the instrument placed on the tumor, and the eye piece detached. This allows the water free exit and the contraction of the bladder firmly implants the tumor against the open end of the instrument and holds it in place until the point of the radium needle can be inserted and the tube driven into the growth. The bladder is then filled with water and a second area of the tumor located. This procedure is repeated until the tubes of radium emanation have been studded throughout the growth on an average of about one to every square centimeter of tumor tissue (Fig. 92).

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Specimens removed from the tumor before radiation were later compared with the tumor removed at operation (Figs. 93 and 94).

The most striking feature of radiated tumors is an extreme fibrosis which produces an extensive walling off, replacement, and destruction of the tumor cell.

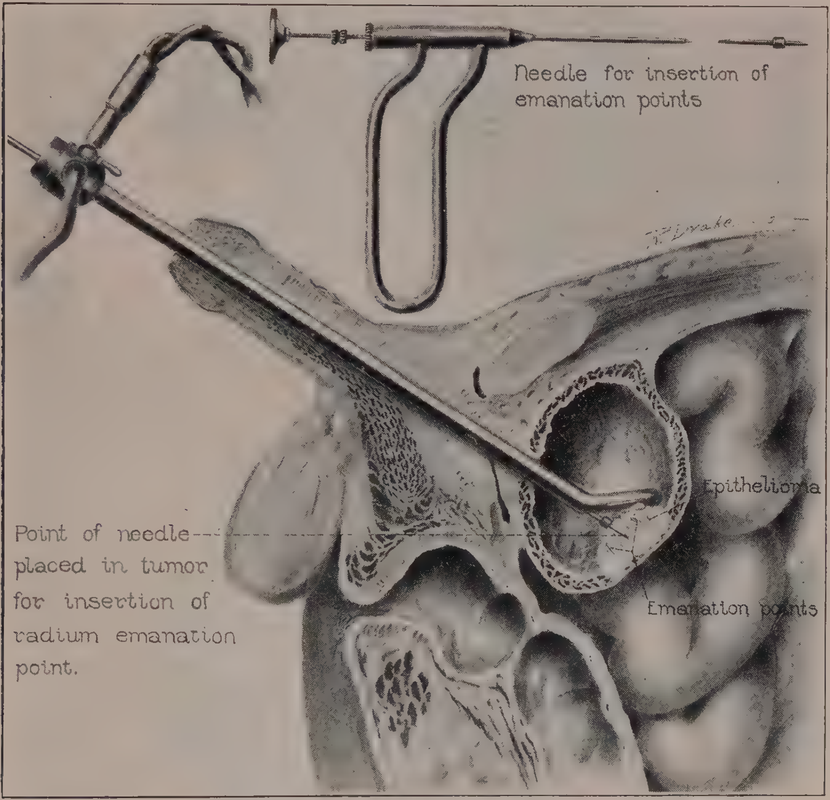
Needle for insertion of emanation points
Epithelioma
Point of needle placed in tumor for insertion of radium emanation point.
Emanation points

FIG. 92.—Insertion of radium points into the bladder through the direct cystoscope.

In some cases the radium rays undoubtedly completely destroyed the proliferating powers of the cells, but in a number of tumors nests of apparently intact malignant cells were found. These cells, generally walled off by extreme fibrosis, were apparently quiescent at the time of operation as a result of the exposure to the radium rays.

The insertion of tubes of radium emanation is a very simple procedure which may be done at the time of the first examination. The small amount of radium rays is slowly discharged and very little reaction is produced. Most tumors of the bladder are superficially placed, thrombosis of the blood vessels develops early, and there is consequently only a slight absorption of necrotic or toxic substances.

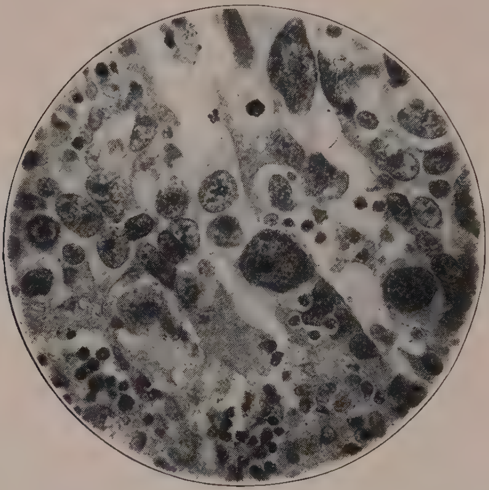

FIG. 93.—Distorted hyalinized atypical cells resulting from exposure to radium emanation. (×350.)

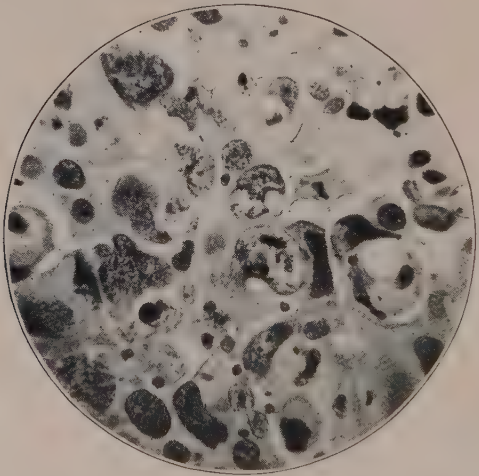

FIG. 94.—Atypical mitotic figures and cellular vacuolization in bladder tumor following exposure to radium emanation. (×350.)

During the period between the insertion of the radium emanations and the operation a daily bladder lavage is given which not only removes any necrotic slough, but also reduces infection of the bladder which is often present.

Emanation tubes are not satisfactory in malignant papillomas, as the loose structure of these tumors does not hold the tubes in place long enough for them to be effective. In the majority of cases in which the emanation tubes have been used the patients have been of advanced age, with wide-spread highly malignant growths requiring extensive operations.

VESICOSIGMOIDAL FISTULAS*

GEORGE D. SUTTON

In 10 per cent of 1,000 proctoscopic examinations made by Sutton at the Mayo Clinic a terminal sigmoid constriction was found; that is, there was an anatomical obstruction to the passage of the proctoscope. In some cases this may have been due to the influence of a short mesentery of the sigmoid and the shape of the sacrum. Such a construction is a probable cause of diseases of the rectum such as acquired diverticula, diverticulitis, localized acute infections, and malignancy.

In all, 256 cases of vesicosigmoidal fistulas have been reported in the literature; 75 per cent of the patients were females and 25 per cent males. From 16 to 33 per cent of enterovesical fistula are vesicosigmoidal in type.

Diverticulitis or peridiverticulitis may be a direct or indirect factor in the production of vesicosigmoidal fistula. Others of importance are age, cachexia, obesity, prolonged retention of feces, flatulence, variation in the size of vessels, muscular deficiency, and congenital predisposition. As pathologic processes resulting from infection through intestinal diverticula McGrath, in 1912, mentioned acute or gangrenous inflammation of diverticula of the sigmoid with perforation and general peritonitis, localized abscess formation, submucous fistula, and fistula involving surrounding viscera, most frequently the bladder.

Of fifty-nine cases of vesico-enteric fistula operated on at the Mayo Clinic between January 1, 1907 and January 1, 1920 thirty-four were of the vesicosigmoidal type. In this series of cases the etiologic infection was in organs adjacent to the bladder, such as the appendix, sigmoid, rectum, and fallopian tubes. Infection of the fallopian tubes was the most frequent cause, being responsible in 36.23 per cent of the cases. Diverticulitis was the cause in 17 per cent. Fistulas due to a primary carcinoma of the sigmoid are easily distinguished from those due to other causes or to malignancy superimposed on an old diverticulitis with recurrent signs and symptoms.

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* Abstract of paper published in full in Surgery, Gynecology, and Obstetrics, 1921, xxxii, 318–327. From the Section on Surgery, Mayo Clinic.

Cystoscopic examination of twenty-six of the thirty-four patients showed a fistulous opening in the posterior wall and dome of the bladder. In the presence of granulations or marked inflammation, the opening may be differentiated from the ureteral meatus by the passage of a catheter and by roentgen-ray plates. The inflammatory changes are due largely to: (1) the size of the fistulous opening, (2) the amount and character of the bowel contents and foreign material passed into the bladder, (3) urethral obstruction and residual urine from stricture or hypertrophy of the prostate, and (4) infective organisms.

Care must be taken during the cystoscopic examination not to pass the catheter through the inflammatory tissue into the peritoneal cavity.

Vesicosigmoidal fistulas may be demonstrated by the cystogram and the use of sodium bromid; methylene-blue injected into the rectum will pass into the bladder and vice versa. Protoscopic examination also may show the condition, though usually with difficulty. Bladder stones may form in the foreign material as a nucleus and add to the discomfort.

The diagnostic features of vesico-enteric fistula are bladder irritability, frequency and dysuria, the passage of gas and feces, and foreign substances in the urine. The prognosis as to life depends on factors of malignancy, peritonitis, metastatic foci of infection, and embolism. The prognosis as to cure depends on the nature, location, and extent of the infective process and the response to proper medical and surgical treatment.

The etiologic factors, cystoscopic findings, and postoperative results in the cases reviewed are tabulated. Twenty-three of the thirty-four patients were cured by operation, six were benefited, and six had recurrences. One of those with recurrence was cured by a second operation. There were four postoperative deaths.

After free drainage has been established proper radical dissection and removal of all diseased tissue are done. All of the patients with vesicosigmoidal fistulas of tuberculous origin were cured, although one had a mildly persistent abdominal and vaginal suppurating sinus. The difficulty in the technic of the operation is the establishment of free drainage and the prevention of the formation of pus pockets in the operative field which is always infected.

PRIMARY TUMORS OF THE URETHRA*

ALBERT J. SCHOLL AND WILLIAM F. BRAASCH

Englisch cites Gurlt's statistics from the Vienna Clinics to illustrate the rarity of primary carcinoma of the urethra. In one series of 16,637 cases of tumors of various organs, no instance of malignant growth of the urethra was noted; in another series including 4,000 cases of disease of the male urinary organs only three were of carcinoma of the urethra. In 358 cases of carcinoma of traumatic origin collected by Löwenthal there were two of carcinoma of the urethra. The occurrence of benign solid tumors in this region is even more rare.

Five patients with solid tumors occurring primarily in the urethra have been treated at the Mayo Clinic. One growth was benign; the other four were malignant. In the male urethra carcinoma is sometimes preceded by long standing premalignant stages. Inflammatory conditions and long standing infection cause metaplasia of the epithelial lining of the urethra. A protective hyperplastic reaction is produced which, in some cases, undergoes malignant changes. Posner collected twenty cases of primary carcinoma of the male urethra; twelve of these patients had previously had urethral stricture. When these tumors develop following long standing infection and stricture their structure is similar to that of tumors forming on other squamous-cell surfaces. The majority of carcinomas which follow long standing infection and trauma are in men of the cancer age and commonly occur at the usual site of stricture formation, in the cavernous and membranous urethra. Occasionally they occur in the penile urethra, and but rarely in the fossa navicularis. Malignant disease is at times associated with urinary sinuses, which generally result from urinary obstruction and extension of the malignant process. In a small number of cases the formation of the fistula is possibly one of the determining factors in the development of malignancy. The irritation of the urine on the cutaneous border and a long standing, low grade infection tend to induce a protective hyperplastic reaction in the epithelial margin. The case of a man with carcinoma of the urethra which followed a long standing urethral stricture is reported herewith.

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* Abstract of paper published in full in Annals of Surgery, 1922, lxxvi, 246–259. From the Section on Urology, Mayo Clinic.

REPORT OF CASE

Case A211630. Mr. G. T., aged forty-eight years, came to the Clinic October 23, 1917. In his youth he had had an infectious urethritis and for twenty years a urethral stricture requiring frequent dilatation. He had a set of urethral sounds which he used often. For three months he had had difficulty in keeping the urethra open, and had noticed a gradually increasing swelling of the perineum. His general health was good.

A hard nodular mass, 2 cm. in diameter, was found in the perineum at the penoscrotal angle. The urethra was markedly obstructed in the region of the mass, but it was possible to pass a filiform bougie to the bladder. The stricture was dilated several times, but rapidly recurred, finally producing almost complete obstruction.

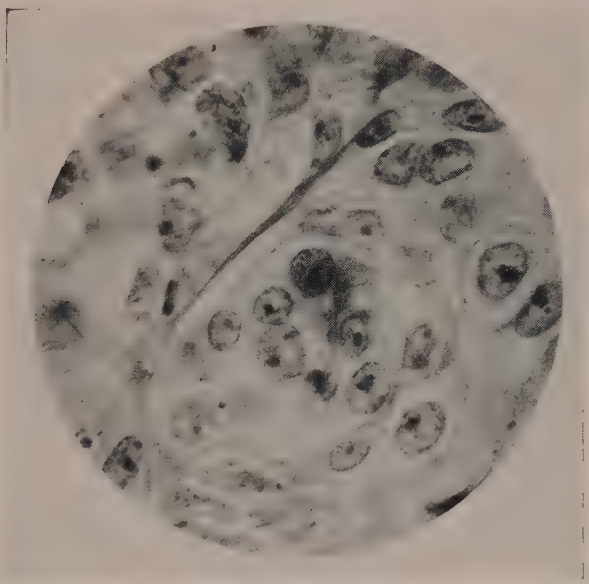

Fig. 95.—Highly malignant cells with prominent nucleoli from carcinoma of male urethra. Tendency toward epithelial pearl formation. (×500.)

At operation a growth 4 cm. long was found at the juncture of the membranous and anterior portions of the urethra. The involved area was completely excised. Later, complete emasculation of the penis and testicles with dissection of the inguinal glands was advised, but refused by the patient. The portion of the urethra removed contained an irregular firm tumor about 3 cm. in diameter. Histologically, the tumor was made up of masses of large epithelial cells with only a small amount of supporting tissue. The cells were irregular, and contained large nuclei and prominent nucleoli. There was slight cellular hyalinization and a few small epithelial pearls. Atypical mitotic figures were common and there was extensive fibrosis and round-cell infiltration. The growth was a well-localized squamous-cell epithelioma of a high degree of malignancy (Fig. 95).

Six weeks later the urethra was reconstructed from a section of the internal saphenous vein. Two months later the area had completely healed save for a persistent perineal sinus. Three hundred fifty milligram hours of radium were applied to the urethra in the region of the scar through the perineal sinus. The patient was alive at the end of five years, but whether or not there had been recurrence was not ascertained.

Primary carcinoma of the female urethra is occasionally confused with carcinoma of the vulva and vaginal wall. Primary carcinoma of the urethra in most cases develops in the mucosa. The primary neoplasm may grow slowly and cause only a few symptoms, as sometimes occurs in carcinoma of the prostate. Attention may be called to the primary focus only by finding a metastatic growth.

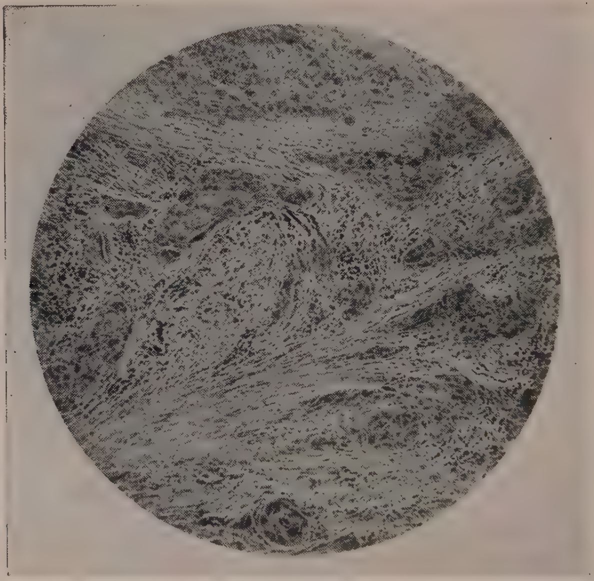

Fig. 96.—Squamous-cell carcinoma of the female urethra; with slight hyalinization and marked fibrosis. (×70.)

Three cases of primary carcinoma of the female urethra were treated. In one case the growth was cauterized with the actual cautery. This patient was without recurrence and perfectly well six years later. The second case was considered too far advanced for surgical treatment. This patient was kept alive in comparative comfort for two years by means of large doses of radium (Fig. 96). In the third case the inguinal glands were involved when the patient was first seen. The urethra and both inguinal areas were exposed to large doses of radium. Eleven months later the patient's urethra was negative and there were no palpable glands. Her general health had improved considerably.

ADENOCARCINOMA

Glandular types of malignancy are seldom observed in the male urethra. Oliver and Clunet reported the case of a man of fifty-two with a small nodular adenocarcinoma 3 cm. from the meatus. Two years later the mass had ulcerated through the corona and extensively involved the glands. Usually the growth appears in the glands at the base of the penile urethra and may be confused with primary urethral tumors. Such extra-urethral tumors cause fewer symptoms; they grow more slowly and generally attain a large size before pain or urinary symptoms develop. They have a tendency to recur after removal. They may completely surround the urethra, but they rarely involve the urethral mucosa. Paquet and Herrmann reported a case of a man of sixty-five who for two years had a small mass between the bulb of the urethra and the rectum. The mass was removed and a tumor developed in Cowper's gland. Kocher noted the case of a man with a similarly located tumor. After four years of growth the tumor was excised, but recurrence followed rapidly. Pietrzekowski reported the case of a male aged nineteen years with a tumor of Cowper's gland of enormous size. Rapid recurrence followed removal in this case also.

Sarcomas generally occur in young persons. They may be pedunculated; they grow rapidly, metastasize extensively, and offer the patient a very poor prognosis. Melanotic sarcoma occasionally occurs in the female urethra. It is extremely malignant and involves surrounding tissue extensively.

Angiomas are found more often in the male than in the female. Only a few cases have been reported. They have a tendency to bleed freely; they cause little pain or urinary discomfort and in most cases respond readily to fulguration.

Fibromyomas are occasionally seen in the female urethra. They are generally covered with urethral mucosa, are small, and cause but few symptoms. They are unattached to the peri-urethral tissues and shell out readily at operation. They bleed only slightly and offer very little obstruction to the urinary stream. They may grow rapidly and attain an enormous size. If they are large they are usually attached to the urethra by a pedicle. Histologically the majority of these tumors are fibromas or fibromyomas. True myomas are unusual.

REPORT OF CASE

Case A60418. Mrs. F. E., aged twenty-six years, came to the Clinic October 23, 1916. For twelve months she had noticed a small mass in the region of the urethra which had increased gradually in size. There had been no urinary disturbance, but straining often made the growth bleed, and at times the urine spattered. During the last four months she had had slight vaginal bleeding between her menstrual periods.

Examination showed a nodular reddened mass 3 cm. in diameter protruding from the urethra. A diganosis of benign tumor of the urethra was made.

At operation an irregular lobulated mass attached by a broad base to the outer half of the urethral mucosa was dissected from the urethral canal. About one-third of the growth protruded from the urethral orifice. The specimen removed was firm and nodular and covered with urethral mucosa.

Histologic examination showed the mass to be made up almost completely of fibrous tissue; no myomatous tissue was found. In some areas interlacing fibrous strands separated the growth into numerous small spaces, some of which were filled with a thinly cellular collagenous material not unlike a mucous polyp.

Three years later the patient had not had a recurrence and was in good health.

Polyps and papillomas of the urethra are often seen. The majority are minute and are usually the result of long standing and tedious urethral infection. They have very little clinical significance and generally respond readily to fulguration or snaring. In some cases the papillomatous growths may be very extensive and completely obstruct the urethra.

THE MALE SEXUAL GLAND IN THE PREVENTION OF CREATINURIA*

MORLEY D. McNEAL

Since creatinuria disappears in boys nearing or at the time of puberty, and does not occur in the normal adult male, but does occur in women, although irregularly, a hitherto neglected factor in its excretion, or perhaps for the prevention of its excretion, obtrudes itself, namely, the influence of the male sexual gland.

In an attempt to determine the effect of castration on creatin excretion, animal experiments were carried on in association with Dr. George H. Jackson, Jr., at the Sprague Institute Laboratory of the Children's Memorial Hospital in Chicago. Three or four castrated rabbits exhibited a definite increase in the amount of creatin excreted. In an attempt to control these castration experiments the vas of each of four rabbits was tied off. Three showed a slight increase of creatinuria, but in one no change occurred. These experimental results are at best only suggestive and further investigation is necessary to determine whether castration exercises a constant influence on the output of creatin in the urine. Such experiments should be repeated on animals that normally do not excrete creatin.

Reid has reported the occurrence of creatinuria in the Chinese eunuch, provided castration was performed before the development of the secondary sex characteristics. The excretion of creatin in three cases of testicular insufficiency has been studied at the Mayo Clinic. One previously healthy patient had excreted creatin in the urine in fairly large amounts since accidental castration at twenty-eight years of age. A second patient, aged thirty-nine, with syphilis of the central nervous system, developed sexual incompetence at thirty-one. This was associated with symptoms of diabetes insipidus, and the urine showed a definite excretion of creatin. A third patient, aged forty-two, who had pea-sized testicles, a typically feminine stature, and a minimum of libido his entire life, also excreted creatin.

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* Abstract of paper published in full in American Journal of Medical Sciences, 1922, clxiv, 222–227. Copyright by Lea & Febiger, Philadelphia. From the Section on Pediatrics, Mayo Clinic.

The three cases have in common, aside from the creatinuria, sexual incompetence of organic nature which occurred in two instances after the development of secondary sexual characteristics. The formation of definite conclusions from these observations is not justified.

TUMORS OF THE TESTICLE WITH ANALYSIS OF ONE HUNDRED CASES*

CHESTER O. TANNER

The exposed position of the testicles, the ease with which they may be investigated by surgical operation, and the early manifestations which any enlargements present, all tend to bring prominently to the attention of physicians definite data for diagnosis and treatment of the various pathologic conditions which may involve these organs.

In respect to the inflammatory enlargements, our knowledge is fairly definite; means of diagnosis are clearly determined, and methods of treatment placed on a rational and well standardized basis. Neoplasms of the testis, however, present a different picture. Not only is diagnosis difficult and made unreasonably late, but often treatment is followed with a blind disregard of the fundamental condition and mode of extension of the tumors. Even pathologists, in all the years in which these new-growths have been studied and classified, are by no means agreed as to their ontology, classification, or proper interpretation. The result is that, as a rule, the patient's welfare is jeopardized, while the surgeon is content with simple orchidectomy, and the pathologist with a general diagnosis of malignant tumor of the testicle.

Malignant disease of any organ or tissue of the body presents such varied growth processes that strict classification and clear-cut prognosis may be impossible.

The testicle is peculiarly adapted to the production of germ cells. Thus, the theoretic classification of tumors of these organs embodies the widest possible range of new pathologic formations. The ovary, whose function is often given a place analogous to that of the testicle, does not present in any closely comparable degree similar problems in tumor ontogenesis. In general, it may be affirmed that tumors of the ovary are more often benign, and even when malignant the degree is less than that of tumors of the testicle.

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* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, 1921. Published in Surgery, Gynecology, and Obstetrics, 1922, xxxv, 562–572. From the Department of Surgery, University of Minnesota, Minneapolis.

Approximately fifty-nine specimens were obtained at the Mayo Clinic, thirty from various hospitals in Minnesota, and twenty from Chicago hospitals. Each tumor was examined grossly and then sectioned so that numerous microscopic sections could be obtained from various areas. In this way all portions of the tumor were examined. Follow-up letters were written to all patients or their relatives when possible, and questions asked as to recurrence following operation, subsequent treatment, present state of health, time of death, and so forth.

It should be borne in mind that the primary lymph nodes draining the testes are those of the lumbar group in front of and by the sides of the aorta and vena cava below the level of the renal veins.

Confusion has existed in the classification of these tumors since the earliest findings were recorded. The following classification is an example:

Myxosarcoma.
Cystosarcoma.
Carcinoma.
Mixed tumor.
Sarcoma.
Medullary carcinoma.
Cystoma.
Cystoid disease.
Teratoma with malignant degeneration.
Dermoids.

Recently Maitland, Hertzler, and others have concurred with Ewing in the belief that all of these tumors are really teratomas and that the so-called pure tumors merely represent a one-sided development of a heterogeneous growth.

Of the 101 tumors in this series, ninety-seven were malignant and four were benign (dermoids). Thirty-five were of the mixed or embryoid type, while sixty-two were of the soft, cellular, medullary type; the latter develop in the interior of the organ. The tunica albuginea is uniformly distended by a solid homogenous tumor without cysts. The color is rose yellow and the consistency is somewhat more firm than that of normal testicular tissue. On cut sections soft, degenerated, whitish zones with the appearance of tuberculosis are often seen. Areas of hemorrhage are common. Before opening the tunica vaginalis this type of tumor looks like an enlarged testicle. The microscopic picture is quite characteristic. It is made up of large, round, and polyhedral cells possessing voluminous nuclei and greatly reduced protoplasm.

The next most common variety, the so-called mixed or embryoid type, contains cartilage, muscle, epithelium with or without cyst formation, nerve tissue, and sometimes bone. Cartilaginous tissue is an element very common in this tumor. Of thirty-five tumors of the series, cartilage was found in seventeen.

Formerly, nearly every testicular tumor was called sarcoma by the surgeon, although it is a type rarely seen. The typical testicular dermoid is composed of a cyst containing hair and sebaceous material, and often teeth. This type is lined by epidermis and is very rare. In the pathologic museums of the medical schools of London, there are only three specimens of testicular dermoids containing hair. There are four in this series.

Another variety of tumor which is still much debated is the so-called chorio-epithelioma of the testis; none was found in this series.

In the following suggested classification only the carcinomatous and mixed tumor types are of clinical importance; the others are included merely to give a place to those rare tumors which undoubtedly do occur.

A. Malignant:
  1. *Carcinomatous*—large cell, large nucleus type undoubtedly closely related to
  2. *Mixed tumor* type
    (a) Tumors containing cartilage, cysts, glands, and so forth.
    (b) Ordinary glandular structure tumors.
    (c) Chorio-epithelioma.
B. Benign:
  1. Dermoid.
  2. Epithelial.
    (a) Adenoma of the seminal tubules as described by Pock and Chevassu.
  3. Mesoblastic.
    (a) Interstitial cell tumors.
    (b) Fibroma.
    (c) Lipoma, myxoma.

Approximately 600 cases of new-growth of the testicle have been reported. The disease occurs about once in 2,000 males. In approximately 300,000 patients (male and female) in the Mayo Clinic, about fifty were found. In the London hospital, records for a period of twenty years referred to sixty-five cases of this disease. During this time 110,000 male patients had been admitted to this hospital.

New growths of the testicle are practically always unilateral. The bilateral malignant growths recorded in the literature are extremely rare and always secondary to tumor elsewhere. Heredity seems to be of little if any importance in this disease. Injury has often been named as an etiologic factor. In this series twenty-two of the 101 patients gave a definite history of injury to the testicle.

The figures in Table 1 confirm the general opinion that practically all cases occur during the period of greatest sexual activity.

RELATIONSHIP TO UNDESCENDED TESTICLE

There is a prevalent idea among surgeons in general that a testis retained within the abdominal cavity is very prone to become malignant and should be removed. My study, however, seems to show that the testicle in the abdomen is relatively immune to malignant changes, whereas the testicle lying in the inguinal canal is more apt to become malignant than the one in the scrotum.

DIAGNOSIS AND SYMPTOMS

Usually the patient consults a doctor on account of a swelling in one side of the scrotum. Nearly always this swelling has been noticed for several months and has gradually increased in size. These tumors are sometimes entirely without pain, but they may be sensitive, and occasionally very painful. In this series there was a definite history of pain in the testicle during some period of the disease in fifty-two cases (52 per cent). The tumors are particularly heavy and firm. In most cases the cord is much larger than that of the opposite side, due to the necessity of a greater blood supply to the part. This is also true in syphilitic testicles and hematoceles. The scrotum contains an ovoid tumor 7 cm. or more in diameter, which is smooth, or slightly furrowed and firm, elastic in consistency, and does not transmit light. It is necessary to bear in mind that hydrocele often accompanies malignancy of the testicle. In a great many patients the family physician had repeatedly aspirated the scrotal sac for hydrocele.

Four diagnoses must be considered: neoplasm, syphilis, hematocele, and tuberculosis. In tuberculosis one is usually aided by the family or personal history. The growth usually increases in size quite rapidly, causes pain, and sometimes fever. It first appears in the epididymis and extends along the vas as small nodules. Later, the testicle is involved and often sinuses break through the skin. Tuberculosis is usually only one manifestation of a generalized genital tuberculosis. The prostate and seminal vesicles may show signs of involvement and tuberculosis bacilli may be found in the urine.

Hematocele cannot be distinguished by its form, consistency, sensibility, or the state of the cord. Two main signs are useful in differential diagnosis; the palpation of the tunica vaginalis and the palpation of the epididymis. If the tunica vaginalis is palpated on the surface of a scrotal tumor it is certain that a hematocele is being dealt with. It will also be impossible to feel the epididymis between the fingers, because it is hidden in the cavity of the hematocele. Exploratory puncture should not be done in such cases. Often a neoplasm is aspirated, blood is obtained, and a diagnosis of hematocele made. In this way proper treatment is delayed, and early spreading of the neoplasm becomes possible. A biopsy is warranted in all cases of doubt.

PROGNOSIS

Of 600 cases collected from the literature in which operation was performed, 465 patients were traced. Of these, 377 (81 per cent) were dead, only 25 (5.5 per cent) were found to be living and well four years or more after operation.

These tumors may be divided, from the standpoint of prognosis, into three types: (1) very malignant (mixed tumor); (2) less malignant (carcinomatous); and (3) benign (prognosis reserved).

The mixed types change rapidly in structure. This is contrary to the behavior of mixed tumors found in the parotid, submaxillary glands, and elsewhere. Of the twenty-two patients with mixed tumors reported in this series only two were alive three or more years after operation, and nineteen (91 per cent) were dead. Of the ten cases in this series in which the tumor contained cartilage all but one patient died, and all the patients died whose tumors contained papillary and squamous epithelial nests.

The carcinomatous type of tumor grows slowly and remains limited for a considerable length of time. It may be eradicated if treated early. Of thirty-nine patients traced with this type of tumor twenty-three were dead and sixteen were living four or more years; a morbidity of 60 per cent. The prognosis is also better in the small tumors in which the cord and epididymis are uninvolved.

The prognosis in the abdominal type of tumor is especially bad, for the majority of patients do not present themselves for treatment until fairly late in the disease, owing to the fact that no symptoms may be noticeable until complications from pressure arise.

Dermoids are benign as a rule, but with two reservations; all such tumors are subject to malignant change, and it is impossible to draw a line between a relatively simple dermoid and a particularly complex mixed tumor.

TREATMENT

Simple castration has been the method of treating such cases for many years, but it has been disappointing from the curative standpoint. This, of course, does not apply to the benign types some of which may be treated by simple removal of the growth and the preservation of the testicular tissue and the others by simple castration. Gross, in his statistics of twenty-six malignant tumors of the testicle, cites three cases of "cures"; two for two years and one for fourteen years. Of the 101 cases in this series, thirty-four were of the so-called mixed type. Twenty-five of these cases were traced and only six were found to be living and well. Three were living six months after operation; one, eight months; one, seven and one-half years, and one, nine years. None has reached the ten-year limit. Of the nineteen patients who died, two lived seven days to two months; two, two to six months; six, six months to one year; three, one to two years; three, two to three years; one, three to four years, and two, four years or more.

There were sixty-two patients with carcinomatous tumors. Fifty-four of these were traced and twenty-three were found to be dead, following castration. Of these twenty-three, one died from seven days to two months after castration; six, two to six months; four, six months to one year; four, one to two years; three, two to three years; three, three to four years, and two, four years or more.

Of the thirty-one living patients, three are living six months to one year after operation; four, one to two years; four, two to three years; five, three to four years; six, four years; two, six years; one, seven years; one, eight years; two, nine years; one, eleven years; one, fourteen years, and one, fifteen years. Thus, fifteen patients are alive four years or more after operation, and three are alive ten years after operation.

Coley's serum has been used following castration in a considerable number of cases. In 1915 Coley reported a series of fifty-two cases treated in this manner and contends that a better prognosis is offered by such treatment than by the radical operation. Of these fifty-two cases, only two showed involvement of the lumbar lymph nodes clinically at the time of operation. Eighteen are dead, fourteen have passed from observation, and eighteen are living. Of the latter, nine have well marked metastasis, and will, in all probability, die; three are alive more than four years since castration, three are alive more than three years, one more than two years, and two more than one year.

Excluding the two inoperable cases and the fourteen patients who were not traced, the remaining thirty-six show a certain mortality of more than 80 per cent, while none of the remaining 20 per cent have lived long enough to be pronounced cured. In my series only six patients were treated by this method. Of these, four (66 per cent) are dead and two (33 per cent) are living seven and nine years after operation. However, these two had tumors of the so-called carcinomatous type and about 33 per cent of these were cured by simple castration alone.

Ten patients received roentgen-ray or radium treatment following castration. Roentgen rays alone were used in six cases, roentgen ray and radium in three cases, and radium alone in one. Of the patients who received roentgen ray alone one is living and well four years after operation; one, three years after operation; one, two and one-half years after operation; one died three months after operation, and two died seven months after operation.

Of the patients who received roentgen ray and radium one is living and well one year after operation; one died three months after operation, and one died seven months after operation.

The patient who received radium alone is living and well six months after operation.

It is thus seen that five of ten patients are dead, and of the six who are still alive only one is living more than four years. Theoretically, the ideal treatment of malignant testicular tumors should consist in the ablation of the neoplastic organ, the lymphatics, and all the nodes into which these lymphatics drain. Any given malignant tumor should be investigated as to its extension upward, and in particular the state of the lumbo-aortic nodes. If a mass can be palpated deep in the abdomen below the umbilicus, the diagnosis is easy. But often cases which are apparently seen early and show practically no involvement of the cord except a slight thickening, are treated by castration, and in a few months marked metastasis in the lumbo-aortic nodes is seen. It is, therefore, fair to conclude that in every case of cancer of the testicle one should regard the lumbo-aortic nodes with suspicion. Complete castration should be followed by a systematic removal of the nodes draining this region.

The first operation of such character was performed by Roberts in 1902. He operated on a patient with recurrent malignancy of the testicle by a median abdominal incision and removed the lumbar nodes. The patient died of peritonitis two months later. The first successful operation of this kind was performed by Cuneo in 1906. He removed four enlarged lymph nodes, one of which showed malignant invasion, and the patient remained well and free from metastasis for more than three years, when he disappeared from observation. Since then numerous surgeons, particularly in France, have adopted this operation.

Bland-Sutton says: "Tradition plays an unconscious part in the acts of the most unconventional surgeon. This is the only explanation I can offer concerning the universal practice among surgeons when performing the ancient operation of castration for malignancy of the testicle in allowing their efforts to be limited by the internal abdominal ring. It is undeniable that the modern method of extirpating the primary growth, the associated lymphatics and the lymph glands, in dealing with cancerous organs has greatly improved the remote results of operation designed for the relief of cancer. This is manifest in the case of the breasts, lips, and labia."

Hinman has collected a total of forty-six cases treated by the radical method. There was a combined surgical mortality in all cases of 11 per cent (three deaths from pneumonia and two from peritonitis). Commenting on this mortality Beer says: "Even though at present the mortality of this operation is much higher than that of simple castration, experience has shown that such is the case with all new operations. The writer feels confident that during the next decade the mortality of this extensive operation will be markedly reduced."

Hinman found that 46 per cent were alive, one for five years, one for four years, five for almost three years, two for more than two years, and eleven for one year or less. There is a probable cure in at least four cases in which the lumbar nodes were invaded with cancer at the time of the operation. Simple castration would not have cured any of these patients and their cure is directly attributable to the early and clean removal of the affected lymph node area.

Within the last two years Hinman has operated on six cases of testicular tumor by the radical method without operative mortality. In four of these cases retroperitoneal lymph nodes containing metastatic tumor masses were removed. The patients are in good health nine months, seven and one-half months, four months, three months, two months, and three and one-half years respectively following operation. Naturally the ultimate result in these cases cannot be known for years. However, the finding of metastatic tumor tissue in the lymph nodes in four cases shows the futility of simple castration. A cure by the radical operation in any one of these four cases will have been due to the early and clean removal of the lymph-draining area.

TECHNIC OF OPERATION

Simple castration is first performed through a high inguinal incision. The cord is dissected out as high as possible and divided on a clamp, preferably with a cautery. The clamp is left in place for traction on the spermatic vessels in the second part of the operation. At this state, if the tumor is found to be malignant on gross or microscopic examination, the second step of the operation is carried out. The incision is prolonged from the high inguinal incision made over the external ring to a point about 1.7 cm. above the anterior superior spine. It then curves upward until it reaches the costal margin at the level of the tenth rib. The incision is carried through the muscle of the abdominal wall until the peritoneum is reached. The cord is traced until it passes through the internal abdominal ring, and then, with the sides of the incision strongly retracted, tension is applied to the cord in order to keep it recognizable. The peritoneum can then be stripped back by gauze dissection without carrying the cord with it. The cord is traced well down into the true pelvis, where it is divided between two ligatures.

The next procedure consists in the dissection of the fascia over a portion of the iliac and psoas muscles, together with the spermatic vessels and lymphatics which it contains, and the removal of the nodes from the inferior vena cava and aorta. Due to the fact that the spermatic vessels spread out above the point where the vas was ligated, it is necessary to make a wide dissection of the fascia on the outer side, and this should extend to the lateral border of the psoas muscle. On the inner side the line of division of the fascia should pass medially, crossing the common iliac at its bifurcation; here the ureter will be found and should be well exposed. The dissection is then carried upward along the inner side of the common iliac vessels to the aortic bifurcation. When the right testicle is involved the inner border is continued over the middle of the aorta; when the left testicle is the seat of the tumor the inner border is carried up along the right border of the aorta, where the inferior mesenteric artery must be carefully guarded. In either case the upper limit is the upper border of the renal veins. Everything between these boundaries must be removed. The spermatic artery can be clamped as it emerges from the aorta and the vein as it enters the renal vein or inferior vena cava. After all bleeding points have been secured the peritoneum is allowed to fall back into place and the wound is closed, with drainage. This is best accomplished by a rubber tube leading to the aortic bifurcation and brought out as in kidney drainage. Hinman advises in cases with apparent metastasis the placing of a small rubber tube or catheter in the end of which is fastened a 50 mg. tube of radium alongside of the rubber drainage tube. In this way metastatic areas may be radiated from above downward by moving the catheter certain distances at intervals of one to two hours.

The radical operation should never be undertaken when abdominal metastasis is recognizable clinically and should be used only in those cases in which the disease is apparently limited. Owing to the deep position of the nodes these cases cannot always be differentiated before operation, and so all in which there is clinically no invasion are suitable for this operation. Before proceeding with the operation diagnosis should be confirmed by examination of the tumor following the first stage of castration. This would prevent further operation in cases of syphilitic testicles in which an incorrect diagnosis had been made. The nonoperative treatment consists of Coley's serum, and radium or roentgen ray, and should be used in all cases which show abdominal metastasis clinically.

SUMMARY

1. New growth of the testicle occurs about once in 2,000 males. The disease is practically always unilateral, involving both sides only as a metastatic growth from the skin, seminal vesicles, and so forth.
2. Trauma as an etiologic factor evidently has some foundation.
3. Practically all tumors of the testicle occur between the ages of eighteen and fifty years, the period of greatest sexual activity.

4. Both testicles are involved with about equal frequency.

5. Undescended testicles within the canal are more apt to become malignant than normally placed organs. Undescended testicles within the abdomen are relatively immune to malignant changes.

6. The average mortality is about 80 per cent, based on a four year postoperative period.

7. In this series the mortality was about 70 per cent.

8. The so-called mixed type of tumor gives a much higher mortality than the carcinomatous type. In this series it was 90 per cent in the former type and 60 per cent in the latter.

9. Tumors containing cartilage and squamous epithelium seem to have a decidedly unfavorable prognosis.

10. The prognosis in abdominal tumors is also very bad, only 6 per cent of a large series of patients being alive and well two years after operation.

11. Radical operation should be performed in all cases in which the disease is apparently limited, that is, in cases without abdominal metastasis clinically.

12. The ordinary operation of castration, even when supplemented by Coley's serum, roentgen rays, or radium, does not yield satisfactory results.

EMPHYSEMA OF THE SCROTUM, THE RESULT OF DIVERTICULITIS OF THE SIGMOID WITH PERFORATION*

FRED W. RANKIN AND E. STARR JUDD

The patient, a male, forty-six years of age, registered at the Mayo Clinic November 11, 1921, complaining of pain and soreness in the left lower abdominal quadrant. The pain, at first sharp, shooting, and confined to the lower left abdomen, later radiated into the perineum and across the entire lower abdomen. The patient had nausea, but no vomiting, fever of 100, no blood in the stools, and no diarrhea or constipation. He had had intermittent attacks for three years, increasing in severity and frequency. Two grains of morphin a day were required for relief. Six weeks before examination he began to have marked frequency and burning, although no blood or gravel was found in the urine. On two occasions he had passed gas from the urethra.

Physical examination was negative. Urine showed albumin 1, erythrocytes 1, and pus 3. Combined phenolsulphonephthalein test was 50 per cent and there was one-half ounce of residual urine. Leukocytes numbered 7,300, erythrocytes 4,550,000, and the hemoglobin was 74 per cent. The roentgenologic diagnosis was obstruction in the sigmoid flexure. On digital examination of the rectum an obstruction was met principally on the right side about 9 cm. from the anal orifice. A tentative diagnosis was made of diverticulitis of the sigmoid attached to the bladder causing a secondary cystitis and producing an intermittent fistula.

Operation November 19, 1921, revealed a mass about 9 cm. in diameter deep in the pelvis and attached to the left wall of the bladder. This was identified as sigmoid with much inflammatory tissue about it. Multiple diverticula of the sigmoid could be demonstrated above the growth (Fig. 97). A loop of ileum was adherent in the mass and was not removed for fear of perforation. The colon above was greatly distended with gas. A resection of the entire mass seemed too formidable an operation for one stage; therefore, a preliminary colostomy was made.

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* Abstract of paper published in full in Surgery, Gynecology, and Obstetrics, 1922, xxxv, 310–312. From the Section on Surgery, Mayo Clinic.

The immediate convalescence was uneventful. The colostomy had not been opened. On the eighth day the patient complained of quite severe gas pain and suddenly noticed that his scrotum began to swell painlessly, but at a noticeable rate. Within two hours it was about 30 cm. in diameter and air crackles were quite distinct. It seemed certain

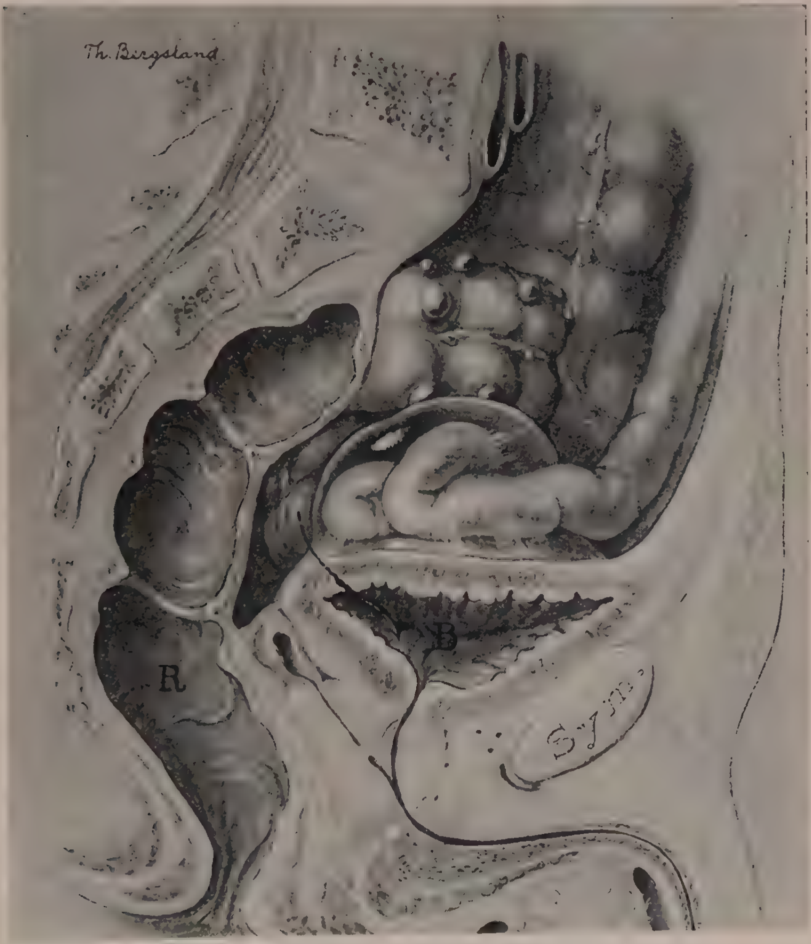

Fig. 97.—Diverticula of the sigmoid above the mass which is attached to the lateral wall of the bladder. The loop of the ileum is adherent. Fistulous opening between the bladder and sigmoid.

that the condition was in no way connected with urinary extravasation, since the patient voided with ease and the physical appearance and feel of the tissues were characteristic. The fact that a fistula was known to exist between the bladder and sigmoid did not explain the condition, since it offered no anatomic basis for such an emphysema. The abdomen was ballooned up with gas and peristalsis was visible. The colostomy was opened and abdominal distention thereby relieved. The emphysema of the scrotum decreased very gradually; two weeks elapsed before it was complete. The patient was none the worse for this unusual complication.

Owing to peculiar anatomic arrangements it seemed highly improbable that gas had made its way into the bladder and thence into the subcutaneous tissues of the scrotum; that another perforation, or leakage from the same one had occurred and had burrowed through the peritoneum and under the fascial layers to emerge in front of the triangular ligament and infiltrate the adjacent subcutaneous tissues, seems the obvious deduction.

METASTATIC CARCINOMA FROM THE PROSTATE OCCURRING IN THE URETEROPELVIC JUNCTURE. REPORT OF A CASE*

ALFRED S. GIORDANO AND HERMON C. BUMPUS

Metastatic carcinoma of the ureters is not a common occurrence, in fact, a careful review of the literature revealed no report of a similar case, The following case is of interest not only because of its rarity but also because it may throw light on the question of the route of infection from the bladder to the kidneys.

REPORT OF CASE

Case A353501. Mr. G. A. T., aged sixty-three years, registered in the Clinic March 24, 1921, complaining of difficulty and frequency of urination of two months' duration. He voided every half hour day and night, and finally, one week before admission to the Clinic, complete retention occurred, and it was necessary to use a catheter. For eight months he had had persistent so-called sciatic or rheumatic pain in the left leg. He had lost 50 pounds in weight.

Examination was negative, save for a hard, nodular enlargement of the prostate gland which seemed to be confined within the capsule. The phenolsulphonephthalein test showed a 33 per cent return of the dye; there was 20 mg. of urea in 100 c.c. of blood.

Roentgenograms of the chest, spine, pelvis, and femurs were negative except for slight increased density in the sacro-iliac region. Radium treatment was recommended, although the history of left sided sciatica indicated periprostatic extension. Since the main symptoms were due to retention, it was hoped that partial prostatectomy following radium treatment might give relief.

After the application of 1,145 mg. hours of radium, the patient developed marked gastric, intestinal, and cardiac symptoms, failed rapidly, and died six days later.

At necropsy there was found carcinoma of the prostate extending into the bladder and metastasis to the periprostatic and perivertebral lymph nodes, the lungs, the left kidney, and left ureter close to the ureteropelvic junction. Histologic examination revealed carcinoma cells in the pulmonary and renal blood vessels (Figs. 98, 99, and 100).

The metastasis to the pelvis of the kidney in this case may be interpreted as illustrating the direct lymphatic connection to the prostate, bladder, and kidneys, and may be considered evidence that infections of the bladder reach the kidney not by the lumen of the ureters but by the lymphatics. However, this does not seem probable, as the lymphatics of the ureters were not involved. Moreover, so far as we know, this is the only case reported in the literature in which carcinoma of the prostate metastasized to the renal pelvis. This extreme rarity should be strong presumptive evidence that direct lymphatic connections between the lower and upper urinary tract do not exist, and that infection does not travel in this manner. Otherwise, with the large number of neoplasms of the bladder and prostate, metastasis to the kidney would occur more often.

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* Abstract of paper published in full in the Journal of Urology, 1922, viii, 445–450. From the Section on Urology and Pathologic Anatomy, Mayo Clinic.

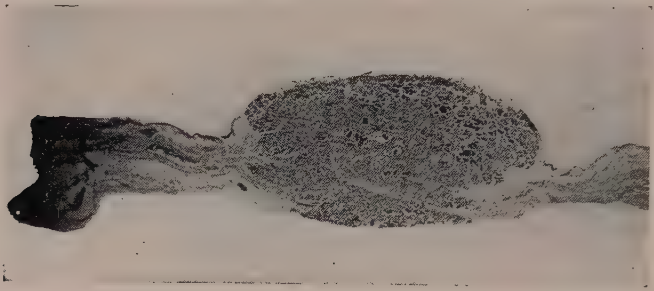

FIG. 98.—Metastatic nodules from the left ureter.

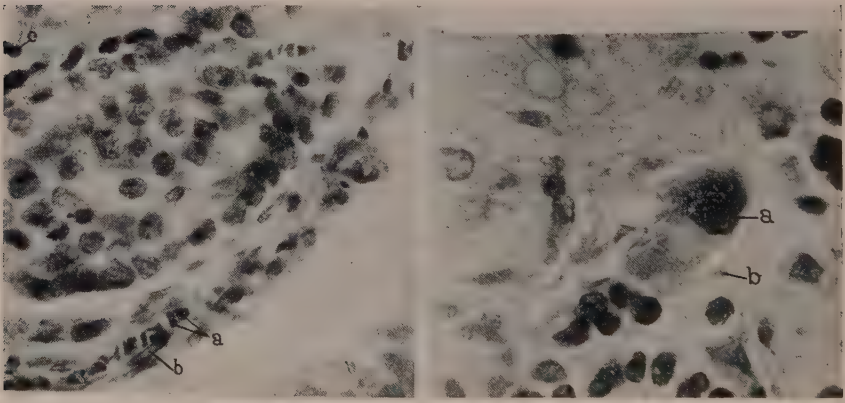

FIG. 99.—a. Large blood vessel filled with and surrounded by carcinoma cells. b. Red blood-cells flattened against the wall of the vessel. c. Mitotic figure outside of the vessel wall. (×500.)

FIG. 100.—a. Carcinomatous cell in blood capillary near the renal infarct. b. Endothelial cell lining the vessel. (×1000.)

In this case the presence of the cancer cells in the blood vessels of the lungs and the metastatic renal infarct would seem to demonstrate that the malignancy was carried through the blood stream to the pelvis of the kidney rather than by the lymphatics, a route probably travelled by many so-called ascending infections.

SACRAL ANESTHESIA IN UROLOGY AND FURTHER EXPERIENCES IN SACRAL ANESTHESIA IN UROLOGY*

ALBERT J. SCHOLL

The structure of the sacrum, in which all the foramina are connected, is especially suited for nerve blocking. Fluid introduced through any of the openings will reach most of the sacral nerves. There are two common methods of anesthetizing the sacral nerves, one by merely injecting novocain solution into the main central canal through the caudal foramina and the other by individual injection of each nerve as it leaves the lateral sacral foramen. The caudal injection is satisfactory for most cystoscopic or endovesical procedures. For the caudal injection the patient is placed face downward. The sacral hiatus which is at the apex of a small triangle is palpated at the lower end of the sacrum; the other angles are formed by the sacral horns. The hiatus is located by sliding the finger from the tip of the coccyx and following the gluteal fold until the converging sides of the apex are encountered. A spinal puncture needle is inserted through the elastic sacral membrane and passed up the canal for a distance of about 3 or 4 cm. (Fig. 101). Injection is made of 30 c.c. of a novocain bicarbonate solution which is freshly prepared for each case. A powder is kept on hand which contains:

Sodium bicarbonate	0.15 gm.
Sodium chlorid	0.1 gr.
Novocain (Metz)	0.6 gr.

This is dropped into 30 c.c. of boiling distilled water which is then removed from the flame. After the solution has been allowed to cool, six drops of 1 : 1,000 epinephrin are added. This solution should be injected very slowly over a period of about four minutes.

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* Abstract of papers published in full in the Journal of Urology, 1921, vi, 149–171, and the California State Medical Journal, 1922, xx, 423–425. From the Section on Urology, Mayo Clinic.

Sacral nerve blocking is very satisfactory in patients with irritable, inflamed bladders, especially of tuberculous origin. Bladders that must be emptied every ten or fifteen minutes may be distended to 150 c.c. during the entire period of the examination with no tendency to discharge.

It is necessary to wait from fifteen to twenty minutes before complete anesthesia sets in; during this time the patient should be sitting up in order to retain the solution in the sacrum. If properly administered, the anesthetic is sufficient in intensity and duration to permit the carrying out of almost any urologic procedure. At the Mayo Clinic this method was carried out in 400 cases (Table 1, page 212).

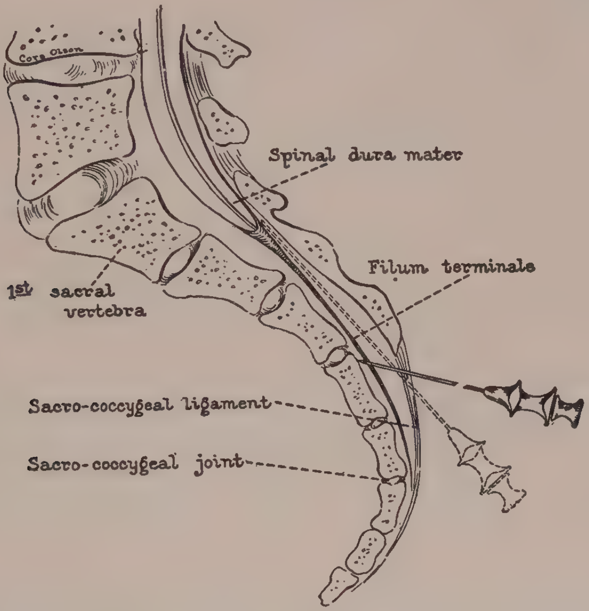

Fig. 101.—Section through the sacrum, showing relation of the needle to the sacral canal and dural sac.

Failures result from various causes. In some patients it is impossible to enter the canal; this generally occurs in patients with small sacrums, in those with hypertrophic arthritis, or with old traumatically distorted pelves. The majority of failures are due to errors in technic or to poor solutions.

Caudal anesthesia is very satisfactory for the examination of in-

TABLE 1

Results of Anesthesia

	Cases.	Satisfactory.	Failures.
Introduction of radium needles through perineum into cancerous prostates	72	69	5
Transvesical treatment of bladder tumors:			
Fulguration	20	20	
Radium emanations	16	16	
Urethral operations	15	14	1
Litholopaxy	21	20	1
Manipulation of ureteral stones	31	31	
Prostatic punch	9	9	
Cystoscopic examination:			
Tuberculous cystitis	63	61	2
Malignant cystitis	48	44	4
Alkali phosphate cystitis	6	6	
Cystitis of pyelonephritis	77	70	7
Irritable bladders	10	9	1
Submucous ulcer	2	2	
Impossible to enter caudal foramen	..	..	8
	400	371	29

fected bladders. Tuberculous bladders which hold only 20 or 30 c.c. of fluid may be distended sufficiently to permit complete examination with catheterization of the ureters without discomfort to the patient.

In malignant bladders a thorough examination of the growth, with the removal of a specimen for histologic study, may be carried out. The growth may be extensively fulgurated over a long period, or radium may be planted in the growth without the patient being aware of the manipulation.

In the cases of litholopaxy a number of patients had large stones removed which required more than an hour of crushing and washing.

One of the most satisfactory features of caudal anesthesia is its almost complete absence of postoperative sequelæ. Several patients complained of nausea and two lost consciousness for several minutes. One patient developed a definite psychosis following the injection which lasted about thirty minutes. Transient sensations of faintness and forceful and increased heart beat were occasionally seen. In no case were delayed or prolonged after-effects observed, and in none was there indication of paralysis of the anesthetized nerves after the general effects of the anesthesis had receded.

Caudal anesthesia gives an excellent relaxation of the lower ureter, and permits the manipulation of ureteral stone; in some cases several large ureteral catheters may be readily inserted to the site of the stone without causing the patient discomfort. Occasionally there is relaxation of the lower ureteral segment and spasm of the upper ureter which causes an impassable angulation.

Sacral anesthesia is simply and easily carried out. It causes very little discomfort to the patient, gives a satisfactory working anesthesia, and rarely produces undesirable after-effects.

CHANGES IN THE MAMMARY GLAND OF THE ALBINO RAT DURING LACTATION AND INVOLUTION*

LeROY M. A. MAEDER

In this study thirty-one rats were used at various stages, twelve during lactation, sixteen during involution, and three virgins as controls. Macroscopic studies were made by observations on the fresh specimens and the total mounts cleared with beechwood creosote. The histologic structure was studied in both frozen and paraffin sections. Frozen sections were stained with hemotoxylin and eosin and with sudan III for fat. Paraffin sections 5 micra in diameter were stained with hematoxylin and eosin, cresyl violet, Mallory's connective-tissue stain, Unna's orcein, and Heidenhain's iron-alum hematoxylin, with and without counterstain of acid fuchsin. Sections of Flemming's fixation were mounted both without stain and with Heidenhain's iron-alum hematoxylin stain.

RESULTS OF INVESTIGATION

1. Macroscopic and microscopic structures of the mammary gland apparently undergo little change during the period of lactation.
2. Amitosis is absent and mitosis rare.
3. The epithelium of the ducts is of one layer during this period.
4. The mammary gland during lactation and early involution presents a somewhat atrophic or undeveloped peripheral zone of uncertain significance.
5. After weaning, very little change is noted during the first two days, the alveoli tending to distend from the accumulation of secreted milk.
6. Secretory activity apparently is not notably diminished before

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Arts, 1921. Published in full in the American Journal of Anatomy, 1922, xxxi, 1–26. From the Department of Anatomy, University of Minnesota, Minneapolis.

the third or fourth day, but variation is noted in different individuals and in different parts of the gland. Secretory activity is not apparent after eight days.

7. After the second day the stroma shows a progressive relative increase in volume, while the parenchyma exhibits a corresponding decrease, the normal resting relation usually being approached by the ninth day.

8. During involution the epithelial acinus collapses and simple atrophy of the cells ensues, followed by pyknosis and karyorrhexis or karyolysis.

9. At the end of involution the structure is apparently similar to that of the resting gland in the adult virgin.

10. Considerable variability is apparent in the rate and character of involution, both in different individuals and in different parts of the same gland. The former may be partly due to variation associated with the estrous cycle.

MASSIVE HYPERTROPHY OF THE BREAST*

LINWOOD D. KEYSER

Clinical and experimental data on factors affecting mammary development and function are reviewed. The breasts develop from a modified group of sudoriparous glands and their development and function are under the control of endocrine forces. Puberty hypertrophy is dependent on ovarian activity. A definite cycle of mammary activity runs somewhat parallel to the menses. There is suggestive evidence that the corpus luteum by its formation, persistence, or regression may influence the activity of the breast in pregnant as well as in nonpregnant states. No good evidence has been adduced that the uterus, decidua, fetus, or placenta are directly related to mammary function.

Massive hypertrophy of the breasts is a deviation from normal development. The process does not suggest a neoplasm, as it is diffuse and seems to affect all portions of the organ uniformly and simultaneously. The age of onset in one-half of the bilateral cases is under eighteen years, the process being associated most commonly with puberty and next with pregnancy. Patients as old as forty-eight years have been reported, although there is a marked drop in incidence as the age increases. The process is bilateral as a rule. When unilateral, both sides of the breast are about equally affected.

Secretory activity of hypertrophied breasts is variable. Usually it is normal, but may be either absent or excessive. The rate of growth likewise may progress uniformly or intermittently. Pain is not common.

The relationship of hypertrophied breasts to the menses, to pregnancy, and to lactation, and their association with pathologic conditions of other sexual organs are considered with citations of typical cases. Spontaneous regression sometimes occurs with or without treatment. The terms "diffuse virginal hypertrophy," "gravidity hypertrophy," and so forth are inexact.

Thickening of the skin, flattening of the nipple, hypertrophy, fibrosis, diffuse fibro-epithelial tumor associated with fibro-adenoma are features described in the literature. Malignancy is rare, but is recorded.

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* Abstract of paper published in full in Surgery, Gynecology, and Obstetrics, 1921, xxxiii, 607–620. From the Section on Surgical Pathology, Mayo Clinic.

Pathologically, most cases fall into two groups: (1) fibro-epithelial (often associated with fibro-adenomas) and (2) adipose. Two cases of each type from the Mayo Clinic series are reported in detail. The patients with fibro-epithelial hypertrophy were a girl of fifteen years and a woman of thirty-six whose hypertrophy began with pregnancy. The adipose hypertrophies occurred in a virgin of nineteen years and a parous woman of forty-one years whose hypertrophy was not associated with pregnancy. The adipose type is rare; only four cases have been previously recorded.

The fibro-epithelial hypertrophies were associated with fibro-adenomas, succulence of the preponderant fatty tissue, rapid proliferative changes in the fibro-adenomas, and reproductive activity in the mammary acini (primary cytoplasia of MacCarty). The acinar groups were invaded and broken up by growing fibrous tissue.

The adipose type was characterized by the relative absence of acini and a preponderance of fat. A few fibrous bands traversing the fat carried a moderate number of acini showing primary cytoplasia. The epithelium in both types was hypertrophied to a variable degree.

The etiologic factors are not clearly understood, but the evidence suggests an endocrine dyscrasia probably of the ovarian type.

To be differentiated in diagnosis are intracanalicular myxoma and fibroma, sarcoma, elephantiasis, and the fatty breasts of obesity.

If spontaneous regression fails to occur after a reasonable length of time, surgical amputation may be indicated.

POSTNATAL CHANGES IN WEIGHT AND STRUCTURE OF THE REPRODUCTIVE TRACT IN THE FEMALE ALBINO RAT*

HJALMAR L. OSTERUD

This study deals with the changes in weight and in general structure of the ovaries, uterine tubes, uterus, and vagina of the albino rat during the period of postnatal growth, primarily from birth to sexual maturity.

The normal growth and variability of the body and of the various systems and organs in the albino rat have been carefully investigated by Donaldson, by Jackson and Lowrey, by Jackson, and by Hatai. In Jackson's and Hatai's work the ovary has been included, but so far as the writer is aware, no study of this kind has been made of the growth of the tract as a whole, including the uterine tubes, uterus, and vagina.

Numerous published researches deal in other ways with the reproductive organs of the rat such as those of Coe, Kirkham, Kirkham and Burr, and Sobotta and Burckhard on the maturation, ovulation, and fertilization of the ovum; Lane-Claypon on oögenesis and the interstitial cells; Belloy on the corpus luteum; Hatai on results of gonadectomy; Frank and Corner and Warren on the corpora lutea, and the formation of deciduomas; Arai on the number of ova; and the extensive series of studies by Long and Evans on the oestrous cycle and allied problems. The complexity of growth during the postpuberal period makes necessary the employment of different methods for its analysis; consequently this later period is dealt with only incidentally.

MATERIAL AND METHODS

A series of 180 female albino rats were used, of which 155 have furnished data with regard to organ weights. In age the rats range from newborn to three hundred days; in body weight, from 2.7 to 294 gm. Thirty had given birth to one litter each, at periods varying from twelve hours to three months before being sacrificed. The remaining 125 animals were virgins, kept isolated from males. The serially sectioned ovaries of thirty-two rats (ranging from 4.6 to 255 gm. body weight) were subjected to a volumetric determination of their various structural components, in an attempt to ascertain the relative part played by each component in the growth of the organ. Jackson's paper method was employed. This consisted of projecting every fifth, eighth, tenth, or twelfth section of the organ, as the case might require, on special paper of uniform weight, outlining the elements desired under uniform magnification for any one series, then cutting out, segregating, and weighing the total amounts of paper representing each of the elements. Thus the percentage volumes of the surface layer, follicular tissue, follicular cavities, interstitial tissue, corpora lutea, and connective tissue stroma can be quite accurately determined.

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* Abridgment of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1922. From the Department of Anatomy, University of Minnesota, Minneapolis.

Zenker's, Fleming's and Bouin's fluids, and formalin were used as fixatives. The entire ovaries and tubes were sectioned serially in paraffn. Of the uterine horns and vagina only a representative middle region was sectioned. Iron-hematoxylin,, Delafield's hematoxylin, and eosin were used as stains.

WEIGHT CHANGES IN THE GROWTH OF THE REPRODUCTIVE TRACT

Growth in weight of the ovaries.—The postnatal growth in weight of the ovaries has been described by Jackson and by Hatai. The data are compiled by Donaldson. With their results the present study is in general agreement. It has been repeated chiefly for purposes of correlation with the rest of the reproductive tract.

By plotting the absolute weights of the ovaries on coördinate paper, it is seen that there are three points in the life of the rat when the growth of the ovaries makes a decided change in rate. These occur approximately at 30, 55, and 140 gm. of body weight. After a brief initial period of relative retardation, the first growth period (from birth to 30 gm. body weight and twenty-five to thirty days of age) exhibits an increase in the weight of the ovaries at a rate greater than that of the body as whole. At birth the percentage weight (ovarian weight divided by body weight) averages about 0.017 per cent of body weight (Fig. 102), agreeing well with Jackson's data. However, variability is great. During the first two weeks the relative weight generally falls below that at birth, individual cases reaching a low level of 0.0057 per cent of the body weight. During the third and fourth weeks the relative weight rises rapidly reaching a value of about 0.030 per cent in rats weighing 28 to 30 gm. and twenty-five to thirty days old.

Arai has shown that the greatest decrease in the number of ova in the rat's ovary occurs in the first twenty-three days of life, after which the rate of decrease becomes markedly less. There is definite correlation between this disappearance of ova and the growth of the ovary, which will be considered in connection with the structural changes occurring at this time. Roughly speaking, by the end of this initial growth period the ovaries have grown twice as much as the body.

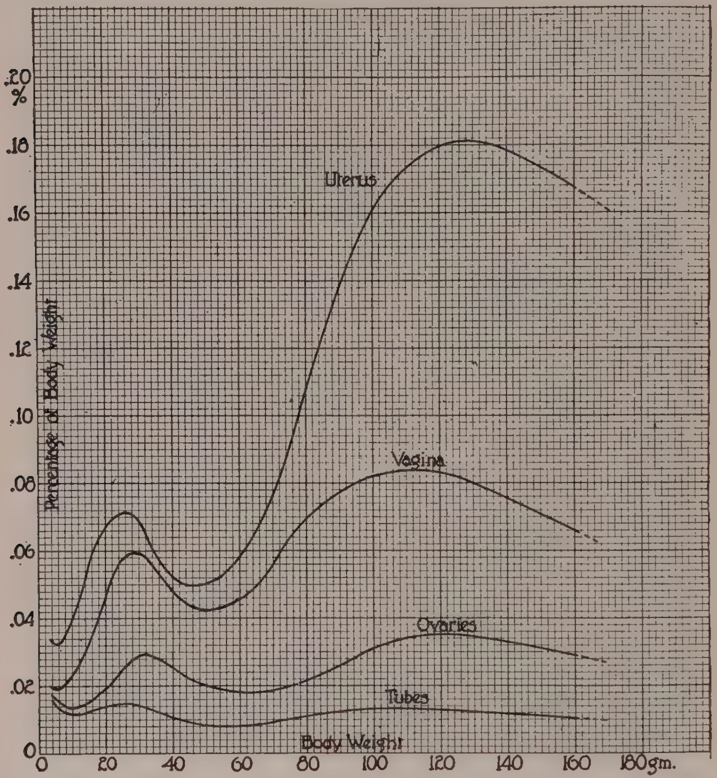

FIG. 102.—Postnatal changes in weight and structure of the reproductive tract in the female albino rat.

From about 30 to 55 gm. body weight, there follows a second period during which the rate of ovarian growth is much diminished. Jackson described this actual decrease in relative weight of the ovaries, his data indicating a drop from 0.030 to 0.015 per cent. The value obtained in the present data is 0.017 per cent. The body as a whole outgrows the ovaries, so that at 55 gm. body weight, the ovaries are of a relative size about equal to that at birth (Fig. 102).

At about 55 gm. body weight a third growth period sets in, another period of acceleration, marking the prepuberal and puberal growth and extending through the establishment of sexual maturity, or until a body weight of 130 to 140 gm. is attained.

Sexual maturity, as expressed by ovulation, appears to fall usually about the middle of this period, in rats of 90 to 100 gm. in body weight. The variation in the ovarian weights now increases markedly so that a field graph of the absolute weights presents a conspicuous scatter. At the end of the period the relative weight of the ovary has reached an approximate mean value of 0.035 per cent.

Beyond this point of 140 gm. body weight, the absolute weight of the ovaries continues to increase variably but the relative weights indicate that the fourth period is again one of retarded growth. The variability in ovarian weights becomes still more marked, attributable to the great variability induced by the structural and functional changes of the ovaries throughout the sexual cycles.

Growth in weight of the uterine tubes.—At birth the ovary is partially enclosed in a peritoneal fold, which, as growth proceeds, gradually covers the ovary, forming finally a thin peri-ovarian capsule, which isolates the ovary from the body cavity. In this capsular fold the uterine tube develops. The complex coiled form of the adult tube is not found at birth; instead the tube has the simple form of an undulating letter C. The early growth of the tube in length is very marked and out of proportion to the distance between its extremities. Consequently a greatly convoluted tube is eventually developed, reaching approximately its complete form in about ten days. By the time sexual maturity is reached, the tube, instead of partially encircling the ovary, has become a compact, coiled mass, much smaller than the ovary, and lying at the side of the hilus. Sobotta found in the mouse, and Long and Evans in the rat, that the peri-ovarian capsule becomes distended with fluid during œstrus.

Growth in weight of the uterus.—It has been found that the postpartum involution of the uterus in the rat is approximately completed at the end of a week following delivery; consequently no data from primiparous rats, prior to the eighth day, are considered in the weight changes of the uterus.

When graphically represented, the weights of the uteri of the rats reveal again a general correspondence in growth with that of the ovaries. The numerical values indicate (by comparison) that the amount of retardation in the second period is less, but that the acceleration during the third period is much greater than in the tubes and ovaries. Comparison of the percentage weight of the uterus at birth with that of the other points in the life cycle seems to indicate that the uterus is relatively underdeveloped at birth as compared with the ovaries.

When the prepuberal growth sets in, the variability increases rapidly, on account of the great fluctuations in weight of the uterus during the sexual cycles. Present data indicate that greatest variability occurs in rats from 160 to 200 gm. body weight. The lowest extremes in normal uterine weight are associated with postpartum involution. Distinct undernutrition also markedly affects the uterine weight.

Growth in weight of the vagina.—In the growth of the vagina the changes in weight follow the behavior of the other generative organs, with corresponding phases. The vagina of the newborn rat is closed and its opening is associated with the first ovulation. A rat at 77.3 gm. body weight was the smallest to display the open vagina. In rats approaching their first ovulation the uterus distends with fluid, a condition which Long and Evans have noted as characteristic of the preœstrous and œstrous phases of the cycle. It seems possible that this fluid may play a part in the opening of the vagina.

Haldeman has carefully described the histologic processes involved in this opening, but does not mention the condition of uterine distention. In intensity of postnatal growth the vagina ranks next to the uterus, exceeding the ovaries and tubes.

Discussion of weight changes.—As appears from the foregoing account, except for minor or doubtful variations, the various parts of the reproductive tract follow a similar type of postnatal growth. After a brief initial period of retardation, growth, up to a body weight of 28 to 30 gm., is very rapid; from 30 to 55 or 60 gm. it is distinctly retarded; from 60 to 130 or 140 gm. again accelerated, with the first ovulation occurring as early as the middle of the period; and finally, after 140 gm. there is a general retardation. Growth in the various parts of the tract is by no means proportionate. It is therefore conceivable that factors, experimental or otherwise, capable of affecting the growth of the generative organs, may have different and varying degrees of influence, depending on the phase of growth of the organs.

In the postnatal growth of the human uterus there occurs during the first two years a very marked involution with which there appears to be nothing comparable in the rat. The relative loss in weight of the rat's uterus is not due to an absolute loss as in the organ of human beings, but merely to a growth slower than that in the body as a whole. Moreover the duration of the low weight level of the uterus in the rat is too short to offer satisfactory correspondence.

STRUCTURAL CHANGES IN THE GROWTH OF THE REPRODUCTIVE TRACT

Structural changes in the ovary.—During the postnatal growth, the ovary undergoes a series of definite histogenetic changes which bear definite relationship to the changes in weight of the organ. The ovary in the new-born exhibits a single-layered germinal epithelium, which is still actively supplying primary ova to a distinct subgerminal zone, inside of which a tunica albuginea is in an early stage of differentiation. The large bulk of the ovary consists of irregular cords and masses of epithelial cells, more or less radially arranged. Primitive ova and indifferent cells are readily made out, the former very prominent because of the nature and arrangement of the chromatin (pachytene diplotene, and dictyate stages of von Winiwarter and Sainmont). Differentiation of the ova and their primitive follicles proceeds from the periphery inward. This early proliferation of primitive oöcytes is interpreted as the end of the fetal proliferation, which soon ceases, and is replaced by a new proliferation of "definitive" oöcytes from which the peculiarly prominent nuclear changes are conspicuously absent. The primitive ova are all destined to disappear by degeneration. The degeneration of ova is already under way at birth, regressive nuclear changes being readily seen in the interior of the ovary. By three days of age the primitive ova have nearly all lost the peculiar nuclear characteristics and by the end of the first week the cell cords become broken up and the primitive ova completely isolated, each with its own follicle. Mitotic figures in the cells of all the ovarian tissues give evidence of increasing growth.

By the end of the first week the proliferation of definitive oöcytes is well under way and a fairly distinct boundary may be made out between the younger definitive oöcytes at the periphery and the older and further developed primitive oöcytes of the interior. This boundary is soon obliterated through the active growth of definitive oöcytes and degeneration or arrested differentiation of the primitive oöcytes. Expansion of the central mass of primitive oöcytes and their follicles becomes more and more conspicuous, and with the increasing atresia of the follicles occurs a rapid proliferation of the interstitial tissue. Arai has shown that the loss of ova in the rat during the first ten days is approximately 20,000 (from 35,000 to 15,000), or nearly two-thirds of the total number.

In spite of this decrease in number of ova, the ovary continues to grow in size and soon does so at a rate considerably greater than that of the body as a whole. Conspicuous in this growth is the development of the follicular apparatus and the increasing production of interstitial tissue.

While follicular growth is plainly increasing, so is also follicular atresia. By the time the rats have reached a body weight of 16 to 19 gm., the larger part of the primitive oöcyte generation has undergone degeneration and a considerable part of the follicular apparatus belongs to the postnatal definitive generation.

By the end of the third week practically every one of the larger follicles gives evidence of atresia. The follicles have become much larger and their walls thinner, chiefly due to the increase in liquor folliculi. From some follicles the ova have entirely disappeared, in others they may be seen floating freely in the fluid of the antrum. Large compact masses of interstitial tissue gradually replace the disappearing follicles. During the third week a spurt of follicular growth again takes place, only to be followed by increasing atresia. Some of the ova undergo a peculiar fragmentation simulating segmentation, even with nuclear inclusions in the several fragments, a condition similar to that described by Kingery in the mouse as an abortive first maturation division.

By the end of the first growth period the amount of follicular degeneration comes to a climax, never again exhibiting these phenomena in such extreme degrees. This corresponds with Arai's findings in his counts of ova, the first great reduction of ova coming to an end at this time. At the periphery of the ovary, however, new definitive oöcytes are still being produced by the germinal epithelium, although perhaps at a reduced rate.

During the first growth period, therefore, the major part of ovarian differentiation has been accomplished, all prepuberal elements have been established, and ova have come near enough to maturity to reveal abortive attempts at maturation, while the ovary has been growing at a rate never to be duplicated and while the ova have been undergoing their greatest reduction in number.

OVARIAN CHANGES IN THE SECOND GROWTH PERIOD

At the beginning of the second growth period the rate of growth is greatly decreased, a decrease correlated with a similar reduction in the rate of degeneration of ova. Arai estimated an insignificant decrease from 10,746 to 10,185 in the number of ova. This period is further characterized by a recovery from the extreme degree of atresia which previously appeared, and by an increased amount of follicular development. Reciprocally there is a decrease in the rate of development of interstitial tissue. The follicles about the middle of this period are conspicuously thick walled, thicker walled for their size than at any other time. In consequence the follicular tissue (stratum granulosum) attains its greatest relative volume during this period. The recovery of follicular growth is, however, only transitory, for atresia sooner or later overtakes even the most robust follicles and by the end of the period degeneration of follicles is again plainly increasing, and again accompanied by an increase in interstitial tissue. The largest follicles, however, attain a size only slightly smaller than that of the fully mature follicle as seen later.

Alternately processes of development and of degeneration apparently hold forth, and progressive and regressive processes are revealed in both follicular and interstitial tissue. One thus observes a complex rhythm of morphologic changes in the ovary which on the one hand bring the ova and their follicles successively nearer maturity, but still fall somewhat short of this goal, and on the other hand maintain a balance, which, seemingly, is both internal, between the ovarian constituents themselves, and external, between the ovaries and the rest of the body. Barring individual variation, the upper and lower ovarian weight extremes appear to bear definite relations to the maximal and minimal phases of structural differentiation.

OVARIAN CHANGES IN THE THIRD GROWTH PERIOD

During the earlier part of this period the structural changes in the ovary are mainly quantitative. Some of the largest follicles exhibit a decidedly robust appearance, with less evident signs of atresia than previously met with. For their size they are not so thick walled as those of younger ovaries. On the whole they give greater promise of attaining maturity than any follicles of preceding growth phases. But atresia is clearly increasing in other follicles and even some of the promising follicles eventually succumb to the degenerative processes. Volumetric determinations show that reduction of follicular tissue is actively under way and that the interstitial tissue is entirely reponsible for the increasing rate of growth of the first half of the period. Arai has shown that at this time there is an increased reduction in number of ova.

The animals, however, attain sexual maturity, some earlier, others later in the period, so that finally some of the follicles and ova come to full maturity and ovulation takes place with formation of corpora lutea. The development of the corpora lutea continues the rate increase begun by the augmented growth of interstitial tissue. Apparently the capacity of the germinal epithelium to produce new definitive oöcytes has by this time been largely exhausted. In one of the rats in which some ova were in the stages of genuine maturation division, distention of the uterus with fluid also occurred and the vagina was still closed.

The first ovulation may not always be perfectly successful as evidenced by failure of the ovum to be extruded, later to be found within the developing corpus luteum. By the end of the third period several ovulations may have occurred and several generations of corpora lutea may be present. The advent of the œstrous cycle introduces complexities into the structure of the ovary, which furnish ample evidence as to the cause of the great variability in weight of the organ. At about 130 to 140 gm. body weight the rate of growth of the ovary rapidly diminishes, apparently in association with a condition of balance within the organ between its progressive and regressive processes.

OVARIAN CHANGES IN THE FOURTH GROWTH PERIOD

The present data indicate that the ovaries continue to grow although at a constantly decreasing rate throughout the fourth period. The largest ovaries were found in a rat of 193 gm. The proportions of the constituent elements vary with the phases of the sexual cycle. The interstitial tissue, which reached its maximal relative development just before the first ovulation, is gradually reduced in amount through active differentiation of the tissue. Follicular degeneration even among large follicles still goes on. There is much in the behavior of the regressive processes, especially in ovaries of virgin animals which have ovulated repeatedly for some time as compared with the ovaries of primiparous animals, which raises the question as to the normality of so much degeneration. Heape in his work on the rabbit thought that increased atresia, which might apparently lead to sterility, was noticeable in the does that were kept away from the males over several œstrous cycles.

CHANGES IN THE VOLUMETRIC RELATIONS OF THE OVARIAN CONSTITUENTS

The surface layer of the ovary (including germinal epithelium, subgerminal zone of oöcytes, and tunica albuginea) totals about 8 per cent of the ovarian volume at birth. By the end of the first growth period this has been reduced to about 2 per cent, which value falls gradually through the other periods. This decrease is primarily due to the loss of young ova and indifferent cells in the exhaustion of the germinal epithelium.

At birth the ova total about 57 per cent of the ovarian volume. This is reduced to about 2 per cent during the first growth period, followed by slow reduction through the other periods.

Follicular tissue increases rapidly to a value of about 34 per cent in rats ten days old, after which the increasing follicular atresia brings about a decided reduction in relative volume to about 22 per cent toward the end of the first period. During the second period follicular volume increases to a maximum of 38 per cent. From this value there is a gradual general reduction throughout the third and fourth periods.

The follicular cavities assume prominent volumetric relations at two points in the growth of the ovary, having increased to about 11 per cent by the end of the first growth period, being then sharply reduced to about 6 per cent, and increasing to about 20 per cent just before the first ovulation, after which there is apparently a slow general reduction, but great variability due to œstrous phases.

The volume of interstitial tissue increases rapidly to about 57 per cent during the first growth period, being the only element of the ovary completely correlated with the great ovarian growth of this period. During the second period the interstitial tissue suffers a relative loss in volume, reciprocal with increase in follicular tissue. In the third period it increases rapidly to a maximum of about 43 per cent just before the first ovulation. The relative volume is suddenly reduced at this point by the development of corpora lutea, but in general there is a slow gradual decrease in volume throughout the rest of life.

The connective tissue stroma plays a more passive volumetric part and increases more gradually from about 7 per cent at birth to 30 per cent at the end of the series.

The sudden development of the corpora lutea naturally affects the relative volume of all other constituents. By the end of the third period a value of about 42 per cent has been reached, which is apparently fairly constantly maintained, with fluctuations above and below this value incident to the influence of the sexual cycle.

Structural changes in the uterine tubes.—While the changes in weight of the uterine tubes, uterus, and vagina show that these organs follow the ovarian type of growth (Fig. 102), none of these undergoes so marked a structural differentiation as is characteristic of the various growth phases in the case of the ovary. Except for changes incident to the œstrous cycle, the growth of the tubes, uterus, and vagina is more quantitative than qualitative.

At birth the uterine tube is very simply coiled. It is then relatively thick walled with a very small lumen lined by a simple columnar epithelium, not unlike that of the adult tube except for absence of cilia, and is similar in structure throughout its length. In the wall the differentiation of lamina propria and muscularis is just barely discernible.

Growth in length is most conspicuous, producing the extensive coiling of the tube in about ten days. In diameter the lower half of the tube increases four or five times from birth to adult, the muscular wall becoming relatively thin, and the upper half only two or three times, its muscular wall becoming relatively thick. When sexual maturity approaches, the usually thin lamina propria hypertrophies and becomes edematous, the epithelial cells of the lining becoming twice their former height in their assumption of secretory activity.

Differentiation of the tubes is, therefore, a gradual process, in which the quantitative changes probably occur in response to the influence of the ovary.

Structural changes in the uterus.—As in the tubes, the structure of the uterus of the newborn rat is very simple. The lumen is, however, relatively much larger. The endometrial epithelium is simple columnar, similar to that of the resting adult uterus. Differentiation into endometrial lamina propria and muscularis is just beginning. In a week's time the main layers of the uterine wall have been definitely established and the formerly more rounded lumen is given a more elongated vertical slit-like form. Diverticula of the lining epithelium begin to grow down as the first fundaments of the glands at about ten days of age. The musculature comes to occupy about half the thickness of the uterine wall, with a thick inner circular and a thin outer longitudinal layer. More slender, tubular glands grow out from the parent diverticula and become slightly coiled, so that by the end of the first growth period when uterine structure is well established, eight or ten glands may be counted in a transverse section.

Until the accelerated growth of the third period sets in there is not much change in the uterus except for a slight increase in the number of glands. When prepuberal growth begins and œstrus approaches, the mucosa undergoes a marked thickening, with distinct hyperplasia and with some hypertrophy, later augmented by congestion. The epithelium of the mucosa and of the glands becomes markedly taller, the cells revealing by their staining reaction the approach of secretory activity. As secretion progresses, the uterus distends with fluid, the epithelial cells increase in width with the stretching of the lining, and the lamina propria and the muscularis become reduced in thickness.

When secretion ceases and the fluid is evacuated, degenerative changes appear in the epithelial cells, followed by desquamation and by immigration of leukocytes. The lumen becomes filled with cell débris and secretion. These changes during the œstrous cycle have been described by Stockard and Papanicolaou in the guinea pig, by Long and Evans in the rat and by Allen in the mouse.

During the fourth period the uterus presents successive series of these structural changes. The uteri of virgin females do not appear to return to a size or structure wholly comparable with that before œstrus, and successive œstrous cycles seem to result in a characteristic summation in weight and structure of the uterus, the uteri sometimes reaching immense size. Compared with uteri of younger animals or with postpartum uteri after involution in animals of about the same age and weight, there are several striking differences. The mucosa is unusually thick (up to four times that of the muscularis) and greatly hyperplastic; the number of glands is markedly increased; the muscularis is only half its normal thickness. The ovaries are filled with old, small, involuting corpora lutea and huge degenerating follicles. The questions arise: are these phenomena common to all female rats during their sexual life or are they the expressions of a response to something abnormal? Is it possible that continued succession of active œstrous cycles induces in the organs of these virgin animals a structural condition inconsistent with proper reproductive function? Heape suggested that withholding the male rabbit from the female during several successive heat periods induces degeneration of the follicular apparatus, making the female liable to sterility. There is much in the structure of both ovaries and uterus in postpartum females to suggest that pregnancy with its subsequent involution restores these organs to a certain balance in structure more like that of younger animals.

Structural changes in the vagina.—At birth the vagina is similarly poorly differentiated. The differentiation of muscularis and lamina propria follow approximately that of the uterus. At birth the vaginal epithelium is two layered, low columnar. By the end of the first growth period it has become three or four layered, and by the end of the second period four or five layered. During the third period the epithelium thickens rapidly to seven or eight layers of cells, assuming a stratified squamous structure. With approach of œstrus the surface layer becomes tall, columnar, and of secretory function. Leukocytes accumulate in the stroma and begin to migrate through the epithelium. The tall superficial cells finally degenerate and desquamate and a large number of leukocytes enter the lumen of the vagina. After this desquamation a typical stratified squamous epithelium remains. The vagina therefore undergoes just as striking œstrous changes as does the uterus. These changes have been described by Morau in the mouse and other rodents, by Stockard and Papanicolaou in the guinea pig, by Long and Evans in the rat, and recently by Allen in the mouse.

DISCUSSION OF THE STRUCTURAL CHANGES

It is clear that it is the ovary in which structural and weight changes are most closely correlated. The ovary probably dominates the growth of the other organs in the way of making the quantitative changes in these follow the quantitative changes in the ovary. In the absence of the ovary (as shown by extirpation experiments) such quantitative changes do not occur.

Proliferation of oöcytes from the germinal epithelium continues approximately up to sexual maturity in the rat, but no separate prepuberal proliferation has been observed.

The great amount of follicular atresia and the large part played by the interstitial tissue in the quantitative growth changes is especially striking in the rat and must be of fundamental significance. From a structural standpoint the interstitial tissue offers no positive evidence as to endocrine function, although the quantitative relations show a parallelism in the growth of this tissue and that of the generative organs, especially in the periods of acceleration. Whatever the forces be that promote or check the growth of the generative organs, to consider these processes apart from the body as a whole, or apart from organs which are known to exert positive influence on the reproductive tract, would therefore appear irrational.

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THE DEVELOPMENT OF FOLLICULAR CYSTS IN THE PREPUBERTY PERIOD AND THEIR RELATION TO EPITHELIAL TUMORS OF THE OVARY*

ERNEST J. COLBERG

The predominance of cystic growth in tumors removed from the ovary is shown by tables from various clinics, 1,383 of a total of 1,494 such growths being cystic. Of 2,140 ovarian cysts it is significant that 16.5 per cent were papillary cystadenomas. This type of tumor shows marked potential malignancy and suggests a possible relationship between cysts of the graafian follicle and epithelial new growths of the ovary. The early age incidence of dermoid cysts suggests the possibility of embryonic origin. The study of the ovary in the child and the development of follicular cysts in the ovary of the child was taken up on this account.

Twenty-four pairs of ovaries were studied in microscopic section. All were from subjects of twelve years or less. The development of the graafian follicle was followed in its various phases. All but one of the twenty-four showed the evidences of development or maturation in the graafian follicle so far as this maturation is carried on in the child. In the ovaries of the newborn in six instances this development was observed in all but one.

In seven instances during the first year developing follicles were found in 100 per cent and follicular cysts or corpora fibrosa in 100 per cent. Four subjects from the second year showed developing follicles and corpora fibrosa; 75 per cent showed macroscopic cysts. In six subjects from two to twelve years, maturing follicles were present in all, although less numerous than in the first two years of life. All showed corpora fibrosa, and sixty-six and two-thirds per cent follicular cysts.

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science, 1922. From the Department of Pathology, University of Minnesota, Minneapolis.

Macroscopic follicular cysts were present in seventeen of the twenty-four subjects examined; thirteen showed cysts of 1 mm. or more in diameter and five showed multiple cysts 2 to 5 mm. in diameter. These cysts may enlarge, due to inflammatory processes, but below 8 mm. they may be considered normal. The development of the graafian follicle, the proliferation of follicular epithelium, the enlargement of the ovum, the formation of the cavity for the liquor folliculi proceeds almost as in the adult, but then instead of rupture and discharge of the ovum and formation of a corpus luteum, there is, in the prepuberty period, a degeneration of ovum and follicle cells and commonly some increase in fluid. All the epithelial elements degenerate. The fluid is then resorbed, the cyst becomes a slit-like space that fills with connective tissue, leaving scars, the corpora fibrosa of the child. All stages in this process were readily traced and in no instance was there evidence of neoplastic transformation in these follicular cysts.

METAPLASIA IN OVARIAN DERMOIDS AND CYSTADENOMAS: REPORT OF THREE CASES*

HAROLD D. CAYLOR AND WILLIAM C. MacCARTY

The relation of metaplasia to neoplastic pathology was studied and discussed by Lubarsch, in 1901, and he mentioned several examples, among them a squamous-cell epithelioma of the gallbladder. He asserted that there is no squamous epithelium in the gallbladder, bile ducts, or neighboring structures, and concluded that such an epithelioma probably results from metaplasia of the lining cells of the organ. Two of the three cases reported were typical of metaplasia in ovarian dermoid cysts and one was a papillary cystadenoma.

CASE OF PAPILLARY CYSTADENOMA

Case A115369. Mrs. S. D. F., aged forty-six years, came to the Clinic in 1914, complaining of long standing menorrhagia and pain, of about four months' duration, in the right lower abdominal quadrants. She had never borne children.

On examination a movable abdominal tumor was found which reached a little above the umbilicus.

At operation a cyst of the right ovary about as large as a seven months' pregnancy was found. The specimen removed consisted of the uterus, tubes, and ovaries. The uterus contained multiple subserous and interstitial fibromyomas, the largest 2 cm. in diameter, the smallest 5 mm. There ware adhesions between the right fallopian tube and the cyst; the left tube apparently was unaltered; the left ovary was small, atrophic, gray, and fibrous. The right ovary was a large cyst, containing multiple papillomas scattered over the inner surface of the wall, the largest being 7 by 5 by 3 cm. and the smallest 5 mm. in diameter. Microscopically, the tumor was made up of papillomas covered by columnar epithelium, typical of papillary cystadenoma of the ovary (Fig. 103).

For seven years the patient was in fairly good health. She returned to the Clinic December 13, 1921, because of frequent, burning and difficult urination and a definite sense of obstruction in the rectum and vagina.

Examination revealed a movable, hard, abdominal tumor pressing on the urinary bladder and rectum, coming well up to the umbilicus.

At the second operation a pelvic cyst about as large as a six months pregnancy was found; the cyst was adherent to the intestines, abdominal wall, sigmoid, omentum, and

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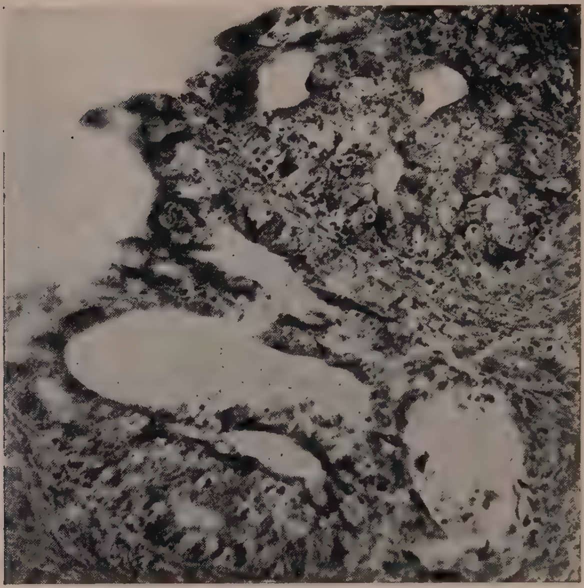

FIG. 103.—Epithelial cells covering the tumor. (×120.)

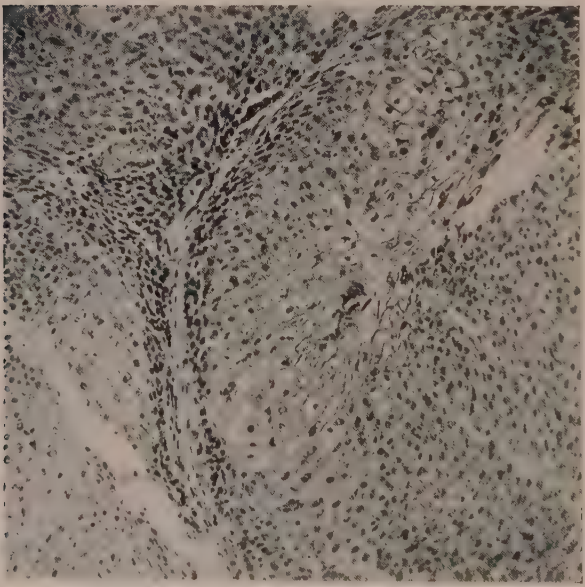

FIG. 104.—Details of the tumor, especially the differentiation of cells. (×100.)

right ureter. The tumor contained serous fluid and in one area, on the inside, there was a firm, raised, flat, grayish brown mass, covering a surface 1.5 by 1 cm. and projecting into the lumen 2 to 3 mm. Histologically, this tumor was composed of epithelial cells growing from the cyst wall in the manner and form of a squamous-cell epithelioma, in places showing definite keratinization (Fig. 104). The whole neoplasm probably arose from a cystic remnant of the papillary ovarian cystadenoma which ruptured during removal at the former operation.

SOLID TUMORS OF THE OVARY*

MERLE R. HOON

A clinical and pathologic study was made of solid tumors of the ovaries which were removed at operation at the Mayo Clinic between January 1, 1910 and August 1, 1921. The series contained fifty-five cases of fibroma, thirty-seven of solid carcinoma, and two of solid sarcoma. The physical, operative, and pathologic findings, and the postoperative results were studied, and conclusions were drawn from questionnaires sent to the patients, and from the physical findings on their subsequent examinations at the Clinic. The patients were treated operatively, and by roentgen ray and radium in case of malignancy.

CONCLUSIONS DRAWN FROM A STUDY OF OVARIAN FIBROMAS

1. Fibromas of the ovary may occur at any age after puberty; they comprise 3.5 per cent of all ovarian tumors (Fig. 105).

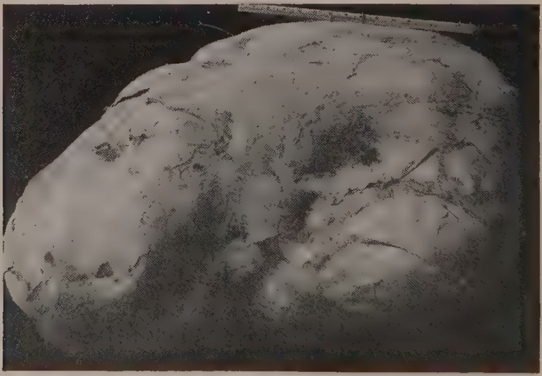

FIG. 105.—Surface view of fibroma 35 x 23 x 15 cm. Weight 13.25 pounds.

2. There may be comparatively few symptoms and the tumor may be present a long time without the patient's knowledge.

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3. Ascites and tumor of the pelvis do not necessarily mean abdominal malignancy.

4. The treatment is surgical. All ovarian tumors should be operated on as soon as diagnosed.

5. The prognosis is good after operation.

6. Subsequent menstrual function is as normal as can be expected following unilateral ovariotomy.

7. Normal pregnancy may occur in patients of child-bearing age, when only one ovary, or one ovary and one tube have been removed.

SOLID CARCINOMAS

The thirty-seven cases of solid ovarian carcinoma are divided into four groups according to the degree of cellular differentiation, and a study of the postoperative results is made in each group (Figs. 106 and 107).

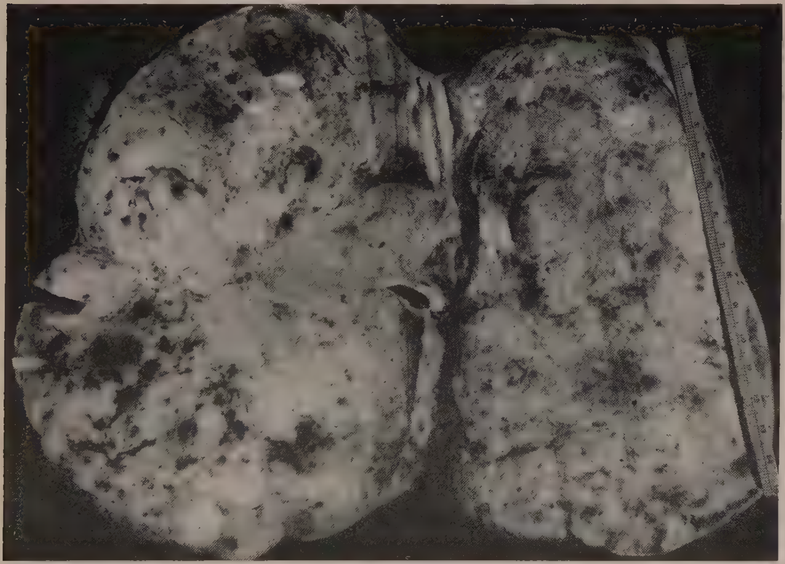

Fig. 106.—Carcinoma of the ovary in a child aged eight years. Specimen 20 x 14 x 9 cm.; cut surface.

CONCLUSIONS DRAWN FROM A STUDY OF SOLID OVARIAN CARCINOMAS

1. Solid carcinoma of the ovary may occur at any period of life from childhood to senility, the most common period being in the fourth and fifth decades.

2. The tumors are highly malignant and are more often primary than the recent literature indicates.

3. Solid carcinoma of the ovary may be bilateral, but in 66 per cent of the thirty-seven cases the tumor was unilateral.

4. Melanotic carcinoma is occasionally primary in the ovary.

5. Melanotic carcinoma of the ovary is highly malignant, as is the same type of tumor elsewhere.

6. The general history is similar to that of ovarian fibromas with the additional symptoms of malignancy, loss in weight, strength, and appetite, and secondary anemia. The growth of the tumor is usually rapid.

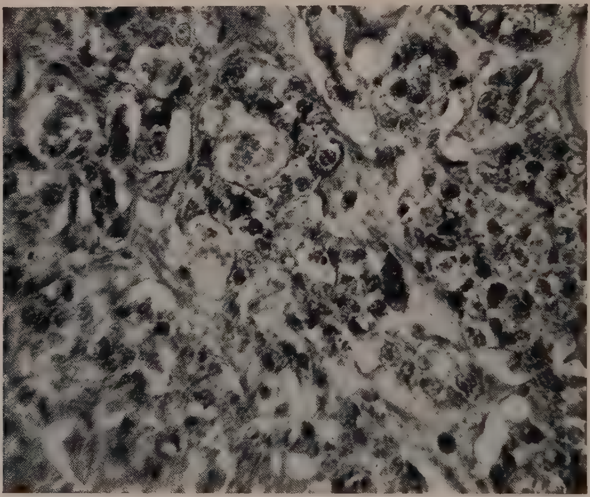

Fig. 107.—Carcinoma, Grade 3. Very slight cell differentiation with a slight tendency to gland formation. (×200.)

7. Ascites cannot be considered a criterion of malignancy as it was present in 35 per cent of the solid carcinomas and in 25 per cent of the benign fibromas.

8. The treatment of solid carcinoma of the ovary is surgical removal, followed by roentgen ray and radium if total removal of malignant tissue is impossible.

9. Metastasis and local recurrence indicate a hopeless prognosis, but palliative treatment may be given by radium and the roentgen ray.

CONCLUSIONS DRAWN FROM A STUDY OF SOLID OVARIAN SARCOMAS

1. Approximately 20 per cent of all ovarian tumors are malignant.

2. Solid sarcoma of the ovary is the rarest type of ovarian tumor; 1 per cent is the approximate incidence.

3. A review of the literature shows that the tumor is most common in young children under three years; it is decreasingly common up to fourteen or fifteen years.

4. The two periods of usual occurrence in adults are during the third decade and after the menopause.

5. Diagnosis and differential diagnosis offer the same difficulties as other solid tumors of the ovary. The diagnosis is seldom made except by the pathologist (Fig. 108).

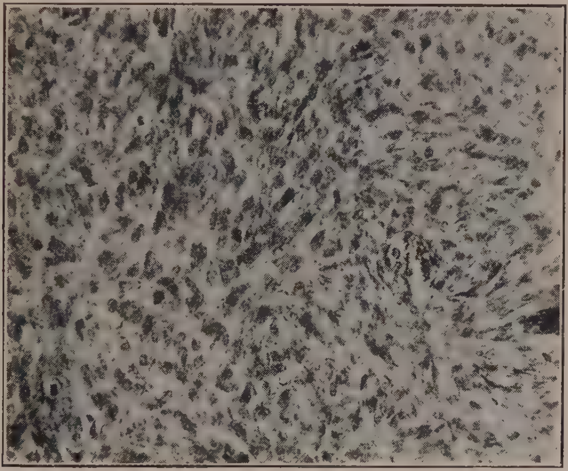

Fig. 108.—Solid (spindle-cell) sarcoma of the ovary. (×200.)

6. The treatment is the same as in cases of solid carcinoma of the ovary, that is surgical removal, followed by roentgen ray and radium if total removal of malignant tissue is impossible, with the possible addition of Coley's serum, which may be of questionable value. If the tumor is unilateral and encapsulated, and if the patient is in the child-bearing period and anxious to bear children, conservative surgery should be employed and only the involved ovary and adjacent tube removed.

7. The prognosis in adults is better than in children.

8. The prognosis in adults is better than in solid carcinoma of the

ovary. The prognosis in children is bad, on account of the high operative mortality, and the early and fatal recurrences.

9. As shown by one case in the series, and by the review of the literature, menstruation may be regular and normal in amount following unilateral ovariotomy for this condition. Normal gestation and delivery may also follow.

10. Solid sarcoma may be accompanied by the same complications as other ovarian tumors.

A CLINICAL STUDY OF CANCER OF THE UTERINE CERVIX: SUMMARY OF THE RESULTS OBTAINED BY VARIOUS METHODS OF TREATMENT*

JAMES W. ROSS

For the purpose of estimating the relative values of various forms of treatment in cancer of the cervix, a study was made of 475 cases seen in the Mayo Clinic between January 1, 1913 and January 1, 1919. The latter date was chosen so that at least three years should have passed since the patients were first seen at the Clinic.

Cancer of the cervix is essentially a local disease. Leitch in a review of 915 necropsies on patients dying from the disease found hydronephrosis in 75 per cent. He estimated the duration from onset of symptoms to death, at twenty-one months. Regional lymph nodes were involved in only 38.36 per cent although this percentage is probably too low if judged by the collected statistics of Döderlein. These patients die of cachexia and uremia rather than extensive metastatic cancer.

The radical abdominal operation, Wertheim hysterectomy, undoubtedly carries a prohibitive mortality in the hands of most operators. We must, therefore, seek an index of the rate of extension of the disease and subject only those patients to extended hysterectomy who have highly malignant tumors and for whom prognosis for ultimate cure is poor. In the past, the cautery and the knife have been recognized agents in treatment, although a multitude of "cures" have been suggested. More recently, radium, and high voltage roentgen-ray therapy have been introduced. Reports of results obtained by many observers using various methods are confusing, owing chiefly to the fact that the estimated stage of the disease is subject to the personal equation of the observer. The effects of radium may be subject also to variation with the dosage, and the method of application.

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* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, 1922. Reprinted from the Canadian Medical Journal, 1922, xii, 722–780, From the Section on Surgery, Mayo Clinic.

In 1912, Percy introduced a method of prolonged cauterization by slow heat and cited cases of patients who had remained free from recurrence for periods varying from three years to eight months. In 1918, he reported cases of sixty-five patients treated by this method, ten of whom (15 per cent) were living from two to nine years after operation. A series of forty-three inoperable cases is reported by Cole. He estimates the average prolongation of life at ten months. In seven instances the patients had lived for periods of three years, and in all amelioration was obtained. Balfour, in 1916, reported favorably regarding this method employed in inoperable cases. Later observations on the same patients showed that cure was effected in only two cases so far as is known.

In 1915, Kelly and Burnam reviewed 213 cases of cancer of the uterine cervix and vagina, fourteen of which were operable and 199 inoperable, and reported cures in fifty-three of the inoperable. Kelly believes that three of every four cases of apparently hopeless cancer can be cured by radium and surgery. On the other hand, Graves, in 1921, said very definitely that radium does not permanently cure. He believes that a few inoperable cases may be rendered operable and the patients may live many months and die of recurrence. But in the treatment of recurrences he believes that radium offers more than any other method. One of his patients treated with radium lived three years and one is now living six years after recurrence. In cases favorable for surgery he does not feel justified in substituting radium. Bailey also obtained good results, but the time was too short accurately to judge the outcome.

In a recent paper Clark was extremely enthusiastic with regard to the effect of radium. In 214 cases of inoperable carcinoma of the cervix, twenty-five patients (11.6 per cent) had lived more than three years, and forty-one others were living more than a year after treatment. Only nine, however, had lived five years. Duncan and Schmitz have reported encouraging results. These operators used larger doses than was the custom at the Mayo Clinic during the period covered by the present review. Clark inserted radium needles into the base of the broad and ureterosacral ligaments, a procedure which has not been carried out in the Clinic. Our immediate results have been encouraging but not sustained in the curative sense. However, it is to be hoped that, when sufficient time has elapsed in which to judge the results of treatment during the past three years, there will be a definite increase in the number of patients cured.

In the present series radium was used in inoperable cases in most instances. These patients received vaginal and intracervical applications of about 700 mg. hours (50 mg. for fourteen hours) three or four times in ten days, with usually one or two rectal applications of 100 mg. hours. They returned at intervals of from two to three months for similar treatment. Now, however, bare radium tubes (wall 0.5 mm. silver) are inserted into the cervix and uterine canal after the redundant growth has been reduced by radiation if necessary. The dose, 700 to 3,000 mg. hours, in favorable cases is given at a single sitting and a total of 9,000 to 12,000 mg. hours is given within a period of three weeks. Roentgen ray is also used, but the high voltage radiation has not been tried. The results here recorded must not then be considered as the final conclusions of the staff of the Mayo Clinic relative to radium and nonoperative treatment.

From reports of various authors it would seem that the Wertheim hysterectomy in operable cases offers the best prospect of permanent cure. Graves in 101 cases had six operative deaths, 27.6 per cent five-year cures, and 16.8 per cent ultimate cures. Still more recently Bonney in 100 cases reports five-year cures of 50 per cent of the eighty patients who recovered from operation. Including inoperable cases he has 26.1 per cent five-year cures. His percentage of operability is 63.5 which agrees with that of Graves (64 per cent), while his immediate mortality has been reduced to 6 per cent in the last fifty cases. Shaw reports similar results but it is yet too soon to judge his results. He advocates the use of radium to render the lesion operable which otherwise would be left to palliative measures.

The operation employed in the series of 475 cases was in some instances a modified Wertheim, less drastic in the extent of dissection than the operation originally advocated. In other instances a much more conservative procedure was carried out, in which a cuff of vagina well beyond the growth was removed with as much of the parametrial tissue as was deemed advisable.

The interval between cautery and hysterectomy which gave the most favorable results was one month; most patients operated on after a greater lapse of time did not obtain permanent relief. It is generally conceded that hysterectomy following radium treatment should be performed after from two to four weeks. This interval allows cellular destruction to take place and antedates fibrosis. Only one patient was radiated one month prior to operation; she lived eight months. However, this procedure is now being carried out in practically all operable cases. Vaginal hysterectomy was performed by the clamp and cautery method.

Besides 475 cases in the series there were eight cases of cancer in the stump of the cervix following hysterectomy and seven cases in which no treatment was given other than explorations, excision of specimens, and simple curettage which are not considered. None of these fifteen patients is living.

Sixty (12.6 per cent) of the 475 patients are living. All have, therefore, lived more than three years. Three hundred twenty-two are dead. There were four operative deaths, one after simple cautery, two after Percy cautery and one after Percy cautery and hysterectomy. In 347 cases the length of life is known (January 1, 1922) (Table 1). Certain of the patients are living and others are dead.

TABLE 1

GROUPING OF CASES

Group.	Patients.	Dead.	Length of life known in.	Living.	Lived more than five years.	Lived more than four years.	Died in less than one year.	Average length of life, years.
1 Early.............	65	26	51	27	11	25	3	3.58
2 Operable..........	142	91	104	24	17	25	26	2.66
3 Inoperable only on account of extension to vagina....	87	64	62	5	5	5	28	1.66
4 Inoperable.........	145	112	105	4	1	3	59	1.08
5 Advanced.........	36	29	25				21	0.58
Total of all groups.	475	322	347	60	34	58	137	

The cases were divided into five groups. This admits of error, as the grouping is based on the operative findings only when they are available and at other times, on the history of the clinical findings. Group 1 contains the early cases in most of which microscopic examination was necessary to establish a diagnosis. In Group 2 are cases which may be considered operable; there is no extension to the vaginal wall, the uterus is movable and the broad ligaments thickened very little if at all. Group 3 is comprised of cases which might be considered operable were it not for extension to the walls of the vagina. Group 4 contains inoperable cases as determined by fixation and infiltration of the broad ligaments. Group 5 is made up of advanced cases, with involvement of bladder or rectum (Table 1).

Thirty-three modes of treatment were used, depending on variations in technic, as for example in the use of the Percy cautery, whether or not the abdomen was opened, and in hysterectomy, whether performed immediately, or later. The methods are grouped under four main headings—surgery, radium, Percy cautery, and simple cautery—subheadings indicate combinations of two or more (Table 2 to Table 6).

TABLE 2

Results of Various Forms of Treatment in Early Cases

Group 1

Treatment.	Patients.	Dead.	Length of life known in.		Living.		Lived more than five years.	Lived more than four years.	Died in less than one year.	Average length of life, years.
Surgery	20	9	16		7		6	9		4.08
With simple cautery	5	1	5	28	4	15	2	3	1	4.0
With radium	11	5	10		6			5		4.0
With simple cautery and radium	4	2	4		2			2		3.75
With Percy cautery	10	4	6		2		1	2	2	2.25
With Percy cautery and radium	3	2	3		1		1	2		3.41
Radium only	5	1	3		2					2.58
Percy cautery and radium	3	2	2		1		1	1		4.0
Simple cautery	1									
With radium	3		2		2			1		3.91
Total	65	26	51		27		11	25	3	3.58

Several factors were common in the series. The average age was practically the same in all groups, forty-eight years; in Group 2, forty-nine years, and in Group 4, forty-seven. The youngest patient was twenty-three and the oldest was seventy-two. All except eleven were married and had borne, on an average, four children. The ages of the youngest children averaged sixteen years. Two of the unmarried women are living. In twelve instances the onset of symptoms occurred during pregnancy and two of these patients are living. Reports from microscopic examination were available in 277 cases. Squamous-cell carci-

TABLE 3

Results of Various Forms of Treatment in Operable Cases

Group 2

Treatment.	Patients.	Dead.	Length of life known in.	Living.	Lived more than five years.	Lived more than four years.	Died in less than one year.	Average length of life, years.
Surgery	26	15	24	9	11	12	2	4.33
With simple cautery	9	7	9	2	1	1	1	2.50
With radium	6	4	6	2		1		2.29
With simple cautery and radium	8	1	4 } 42	3 } 12		1	1	2.66
With Percy cautery	27	21	20	4	4	7	3	3.08
With Percy cautery and radium	8	3	3	1		1	1	2.33
Radium only	21	16	17	2		1	8	1.50
Percy cautery	23	15	14	1	1	1	6	1.66
With radium	2	2	1					2.58
Simple cautery	3	2	2				1	0.66
With radium	9	5	4				3	0.75
Total	142	91	104	24	17	25	26	2.66

TABLE 4

Results of Various Forms of Treatment in Group 3

Treatment.	Patients.	Dead.	Length of life known in.	Living.	Lived more than five years.	Lived more than four years.	Died in less than one year.	Average length of life, years.
Surgery	6	2	4	2	3	3		4.33
With simple cautery	4	4	3		1	1		2.91
With radium	1		1	1				3.91
With simple cautery and radium	1		1 } 10	1 } 3				3.0
With Percy cautery	5	1	2	1	1	1		3.75
With Percy cautery and radium	4	3	3				1	2.20
Radium only	39	30	26				15	1.0
Percy cautery	12	11	10				4	1.66
With radium	2	1	1					3.50
Simple cautery	6	5	5				3	1.16
With radium	7	7	6				5	0.83
Total	87	64	62	5	5	5	28	1.66

TABLE 5

Results of Various Forms of Treatment in Inoperable Cases

Group 4

Treatment.	Patients.	Dead.	Length of life known in.	Living.	Lived more than five years.	Lived more than four years.	Died in less than one year.	Average length of life. years
Surgery	3	3	3				1	1.58
With simple cautery	5	3	3		1	1		3.00
With radium	7	5	6	1			2	1.50
With simple cautery and radium	1	1	1 } 16	} 1				2.50
With Percy cautery	5	5	5				2	1.58
With Percy cautery and radium	1	1	1					2.50
Radium only	57	42	40	2		1	22	1.12
Percy cautery	32	25	22				17	0.70
With radium	11	9	7				3	1.16
Simple cautery	9	8	7				5	0.66
With radium	14	10	10	1		1	7	1.24
Total	145	112	105	4	1	3	59	1.08

TABLE 6

Results of Various Forms of Treatment in Advanced Cases

Group 5

Treatment.	Patients.	Dead.	Length of life known in.	Living.	Lived more than five years.	Lived more than four years.	Died in less than one year.	Average length of life, years.
Surgery	1	1	1				1	0.91
With Percy cautery and radium	1	1	1				1	0.83
Radium only	11	8	5				3	0.81
Percy cautery	11	9	9				8	0.50
With radium	2							
Simple cautery	7	7	6				5	0.58
With radium	3	3	3				3	0.41
Total	36	29	25				21	0.58

noma was found in 249, and adenocarcinoma in twenty-eight. The preponderance of the former, 89.9 per cent, is slightly higher than that given by Ogata (87.7 per cent).

If the cases in Groups 1 and 2 are considered, the percentage of operability is 44, which is somewhat lower than that of Bonney, Graves, Cullen, and others. If cases in Group 3 are included the percentage is raised to 62. Some of the cases in this group proved operable (Table 4).

The average duration of symptoms in each group before the patient sought advice shows a gradual increase in the successive groups. In Group 1 it was 4.6 months; in Group 2, 6.7 months; in Group 3, 6.8 months; in Group 4, 7.6 months, and in Group 5, 11.2 months. This illustrates how a short delay may carry a patient beyond the possibility of operative aid. In fifty-two cases there was delay owing to the physician's failure to recognize the condition. This demonstrates two points: (1) the disease was sufficiently advanced in most cases to be recognized, and (2) a diagnosis was not made and should have been made in certain cases. The patients might have been saved an average of six months of valuable time had a biopsy been made.

In reviewing the results, the normal death rate for women of this age must be borne in mind. It is estimated that forty-three of the 475 would have died during the nine year period.[15] Tables 1 to 6 will show the results obtained. The number of patients treated whose span of life is known, the number surviving four and five years, and the number who died early (within the first year) serves to show the efficacy of the various treatments. If, therefore, under any given treatment we can show a large number of patients who lived four and five years and a small number of early deaths, I think it will be conceded that this treatment is of distinct value as compared with one showing the reverse.

In a few instances the diagnosis of cancer was not confirmed microscopically, but in all, the tumors were clinically malignant. This applies more particularly to the cases in which radium was used in the earlier years. Since in some of the patients who died the nature of the growth was not known, and it was impossible from the replies received to establish whether death was due to cancer or to other causes, it is reasonable to assume that some of the patients living, who had no microscopic findings, had cancer. In the cases in which the patients are living diagnoses were positive in all except seven (Table 7). I have examined specimens of tissue removed in forty of these and I am indebted to Dr. Broders for confirmation of my findings. These specimens were studied from the histologic standpoint to determine if their structure contributed in any way to the survival of the patients concerned. The epitheliomas were graded according to Broders' classification on a

TABLE 7

Treatment, Length of Life, Clinical Involvement, and Pathologic Findings in Sixty Living Patients

Treatment.	Patients living.	Years since treatment.	Clinical group.	Pathologic diagnosis.
Total abdominal hysterectomy	3	8	2	Epithelioma*
	1	6	3	Epithelioma
	3	5	2	Epithelioma
	1	4	1	Adenocarcinoma
	1	3	1	Epithelioma
Vaginal hysterectomy	1	8	2	Epithelioma
	1	8	3	Epithelioma
	1	7	2	Adenocarcinoma
	2	6	1	Epithelioma
	2	5	1	Epithelioma
	1	4	1	Epithelioma
	1	3	2	Epithelioma
Simple cautery and later hysterectomy	1	8	2	Epithelioma
	1	7	1	Epithelioma
	1	5	1	Epithelioma
	1	4	1	Epithelioma
	1	3	2	Epithelioma
Simple cautery and immediate hysterectomy	1	3	1	Epithelioma
Total abdominal hysterectomy and radium	1	4	1	Epithelioma
	1	4	2	Epithelioma
	1	3	1	Epithelioma
	1	3	3	Epithelioma
	1	3	4	Epithelioma
	1	3	2	Epithelioma
Vaginal hysterectomy and radium	2	4	1	Epithelioma
	2	4	1	Adenocarcinoma
Simple cautery and total abdominal hysterectomy and radium	2	3	2	Epithelioma
	1	3	3	Epithelioma
Simple cautery and vaginal hysterectomy and radium	2	4	1	Epithelioma
	1	4	2	Epithelioma
Percy cautery and later hysterectomy	2	7	2	Epithelioma
	1	6	2	Epithelioma
	1	6	3	Adenocarcinoma
	1	4	1	Epithelioma
Percy cautery and immediate hysterectomy	1	5	1	Epithelioma
Percy cautery and vaginal hysterectomy	1	3	2	Epithelioma†
Percy cautery, later hysterectomy and radium.	1	4	2	No specimen
Percy cautery, immediate hysterectomy and radium	1	5	1	Epithelioma
Radium only	1	4	2	No specimen
	1	3	1	No specimen
	1	3	2	Epithelioma
	1	3	2	No specimen
	1	3	3	Adenocarcinoma
	1	3	3	No specimen
Percy cautery only	1	6	2	Epithelioma
	1	7	1	No specimen†
Simple cautery and radium	1	4	1	Epithelioma
	1	4	3	No specimen
	1	3	1	Epithelioma

* One had cautery and radium for recurrence.

† Radium for recurrence.

scale of 1 to 4. Six (16.6 per cent) were in Grade 2; twenty (55.5 per cent) in Grade 3, and ten (27.7 per cent) in Grade 4. Of the four adenocarcinomas studied one was of particular interest in that it showed marked metaplasia (Figs. 109–112). From these findings it is apparant that even in the case of patients who survive, the tumor is usually of a very malignant type, and complete destruction of the growth must be accomplished early if good results are to be obtained.

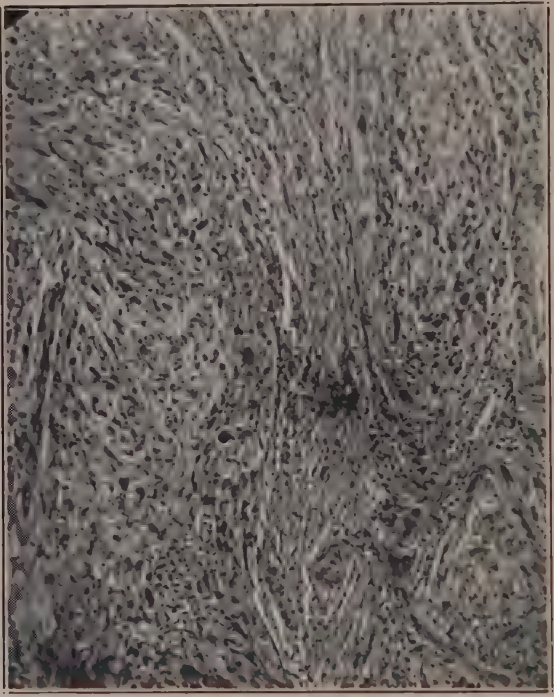

Fig. 109 (Case A129862).—Squamous-cell carcinoma of the cervix, Grade 4. Active cells with no tendency to differentiation. Patient living and well five years and ten months after total abdominal hysterectomy. (×100.)

The length of life under various treatments brings out several interesting facts (Table 8), although the percentages are based on numbers much too small to render them of value other than comparative. It will be seen that the efficacy of vaginal hysterectomy in certain cases is indisputable. Of the nine living patients treated by this method, most had early lesions (Table 7), although one had extension to the vaginal wall (Group 3). Another point well illustrated, if we accept the sup-

TABLE 8

LENGTH OF LIFE OF PATIENTS UNDER VARIOUS TREATMENT

Treatment.	Patients.	Length of life known in.	Living.	Living five years.		Living three years.		Died after three years.
				Patients.	Per cent.*	Patients.	Per cent.*	
Total abdominal hysterectomy	25	24	9	7	30.4	9	39.0	4
Vaginal hysterectomy........	29	23	9	7	30.4	9	39.0	4
Amputation of cervix.........	2	1						1
Simple cautery and later hysterectomy..................	15	12	5	3	25.0	5	41.0	1
Simple cautery and immediate hysterectomy..............	8	6	1			1	12.0	2
Total abdominal hysterectomy and radium†...............	15	14	6			6	43.0	
Vaginal hysterectomy and radium.....................	10	9	4			4	44.0	1
Simple cautery and total abdominal hysterectomy and radium..................	9	6	3			3	50.0	1
Simple cautery and vaginal hysterectomy and radium......	5	4	3			3	75.0	1
Percy cautery and later hysterectomy.................	31	25	5	4	16.0	5	20.0	5
Percy cautery and immediate hysterectomy.............	13	6	1	1	16.0	1	16.0	
Percy cautery and vaginal hysterectomy................	3	2	1			1	50.0	
Percy cautery, later hysterectomy and radium..........	7	6	1			1	16.0	2
Percy cautery, immediate hysterectomy and radium......	10	5	1			1	20.0	
Percy cautery only...........	81	57	2	2	3.5	2	3.5	3
Percy cautery and radium....	17	9						1
Simple cautery..............	26	20						
Simple cautery and radium....	36	25	3				12.0	
Radium only................	133	91	6			6	6.7	4
Total.....................	475	347	60	24	7.0	57	16.6	30

* Percentages in this table are based on cases wherein length of life is known. They thus favor small groups and those from which a large number are excluded on account of insufficient data.

† Radium was first used here in 1915.

position that similar numbers of tumors of like potentialities are present in the various minor groups, is the fact that delayed hysterectomy gave better results than immediate hysterectomy in conjunction with simple cautery and Percy cautery. Furthermore, total abdominal hysterectomy and vaginal hysterectomy, when supported by radium, gave almost identical results, which were apparently slightly better than from either agent alone.

The results of treatment by radium were disappointing. Of 133 patients so treated only six are known to be living; on the other hand, three living patients were treated by cautery and radium. These results must not be given too much weight or used to condemn the method, for the majority of patients obtained inestimable relief, which could not have been given by any other means. The dose used at that time was later found to be too small.

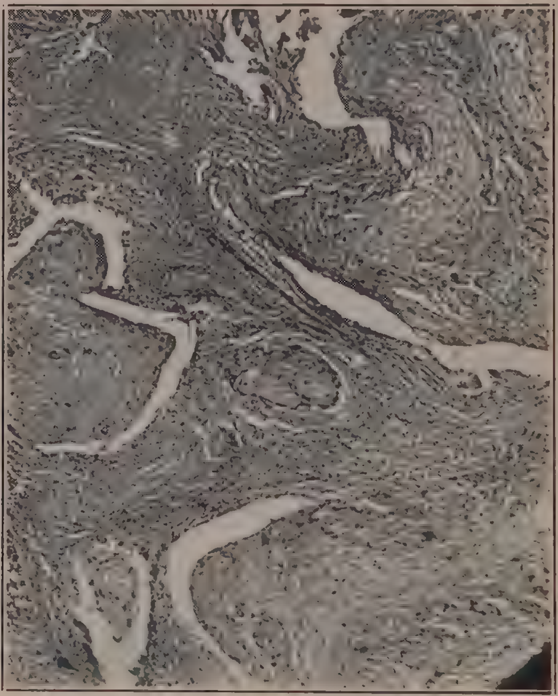

FIG. 110 (Case A147230).—Squamous-cell carcinoma of the cervix. Grade 2. Differentiated and undifferentiated cells in about equal proportions. Patient living and well five years and ten months after total abdominal hysterectomy. (×50.)

The Percy cautery proved curative in only two early cases, although palliation was effected in the remainder, as cited by Balfour in an earlier review of some of these cases.

Twenty patients of Group 1 (Table 2) were treated by surgery alone. Information relative to length of life is lacking in four instances. Nine are known to be dead and seven living; no patient died within the first year. Nine were living four years after treatment and six were living after five years. If these results are compared with those of other methods, and the degree of involvement indicated by the group is considered, a fairly accurate estimate may be made of the relative values of the methods in different stages of the disease (Tables 3, 4, 5, and 6).

The point may be raised that these cases are not accurately grouped, else why do we find any cases in Groups 1 and 2 treated by other means than surgery. On account of factors such as obesity, cardiac decompensation, and the personal considerations of the patient, some early cases were treated by radium. On the other hand, the probable accuracy is borne out by the gradually increased mortality, the shorter period of life, and the longer duration of symptoms in the higher groups.

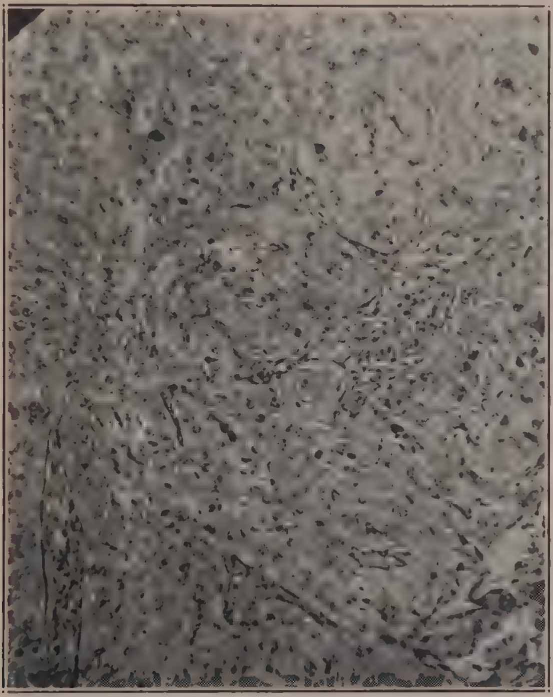

Fig. 111 (Case A166324).—Squamous-cell carcinoma of the cervix, Grade 3. Active cells with small area of keratinization. Patient living and well five years and four months after Percy cautery and immediate abdominal hysterectomy. (×100.)

Of the eleven patients of Group 1 who lived more than five years, ten were treated surgically. Two of the three treated by radium who have been traced were living three years later. The third lived one and one-half years.

Both of those treated by simple cautery and radium are living; one three years and the other four years after treatment.* It is thus apparent that in early cases the various types of treatment gave similar results; it remains for time to prove the durability of results wherein radium was employed.

In cases in Group 2 (Table 3) the Percy cautery and radium yielded approximately the same early mortality; the former method yielded one five-year cure and the latter one four-year cure. The combination of radium, cautery, and surgery in this group proved equally efficient to, if not slightly better than, surgery alone. The incidence of early deaths is higher, but four of the seven are living, while only nine of twenty-four wherein surgery alone was used survive.

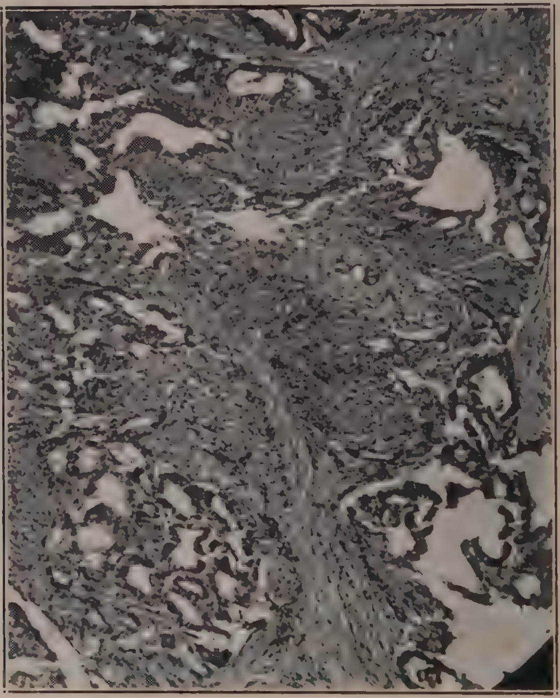

Fig. 112 (Case A245369).—Adenocarcinoma of the cervix showing metaplasia. Patient living three years and one month after vaginal hysterectomy with recurrence. (×50.)

Cases in Group 3 are of special interest. Of the five surviving patients, all received surgical or combined treatment. The use of radium as an adjunct gave the best results; when used alone the results were disappointing.

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* In making a special sub-heading for those receiving cautery and radium, I am reducing the number treated by radium reported by Stacy in 1920.

In cases of Group 4 only patients who received radium alone or in combination survive. Seventeen of twenty-two on whom the Percy acutery was used died within the first year; while only twenty-two of forty on whom radium alone was used died in this period.

In cases in Group 5 radium again showed slight superiority over surgery in prolongation of life. Only three of five patients died in less than one year. Its palliative effect is universally recognized.

Fistulas resulted after treatment in forty-six cases, 9.7 per cent of the entire series. There were twenty-one rectovaginal fistulas, thirty-five vesicovaginal, and there was one vesicosigmoidal fistula. The largest number followed Percy cautery, but this may be due in part to the fact that the abdomen was not always opened to control the uterus and to estimate the degree of heat. The incidence is shown in Table 9.

TABLE 9

THE INCIDENCE OF FISTULA FOLLOWING VARIOUS TREATMENTS

Treatment.	Patients.	Fistulas.			Total.	Total per cent.
		Rectovaginal.	Vesicovaginal.	Vesicosigmoidal.		
Surgery	56	1	2		3	5
Surgery and simple cautery	23		4		4	18
Surgery and radium	25	2	2		4	16
Surgery and Percy cautery	47	3	2		5	11
Surgery, Percy cautery, and radium	17		2	1	3	18
Radium	133	8	9		17	13
Percy cautery	81	7	13		20	24 (high)
Simple cautery and radium	36		1		1	3
Total	418	21	35	1	57	13.6

Eleven patients had two fistulas which makes the incidence 9.7 per cent in the series (475 cases).

CONCLUSIONS

1. In very early cases of cancer of the uterine cervix treatment by surgery alone gives good results. Surgery in combination with radium gives slightly better results than surgery alone.

2. In operable but not early cases, treatment by surgery alone or combined with radium gives the best results. Radium alone or Percy cautery alone are of equal value and both less efficient. If radium is not available, Percy cautery should be used.

3. In cases considered inoperable because of extension to the vagina, surgery gives the best results and radium is disappointing.

4. In inoperable cases radium, alone or in combination with cautery or surgery, is the only effective agent.

5. In advanced cases radium is superior to all other methods, but not curative.

6. The incidence of fistula is higher with Percy cautery than with any other method.

Note: Reports received subsequently credit another three-year cure to radium and an eight-year cure to vaginal hysterectomy in Group 1, and further establish the value of hysterectomy when supported by radium or Percy cautery.

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THE MORPHOLOGIC HISTOLOGY OF ADENOCARCINOMA OF THE BODY OF THE UTERUS IN RELATION TO LONGEVITY: A STUDY OF 186 CASES*

ARTHUR E. MAHLE

In this series of 186 cases of carcinoma of the body of the uterus attention has been directed especially to the study of the degree of malignancy based on the degree of cellular differentiation. The series includes only those cases observed between January 27, 1905 and January 21, 1919, in which specimens were available for study, and could be accurately demonstrated, grossly and microscopically, to be of true carcinoma. The number does not, therefore, include all cases in which hysterectomies for carcinoma of the fundus of the uterus were performed during this period.

It was noted in the records that 855 cases of carcinoma of the uterus were observed between January 1, 1910 and January 1, 1919; 70.3 per cent were in the cervix, and 29.7 per cent were in the uterus.

There are various pathologic classifications of carcinoma of the uterus. Kaufmann divides them into those which arise from the surface epithelium, and, the more common type, those which arise from the glandular epithelium. Under the latter he classifies, first, the so-called adenoma malignum, found most often in the uterus but sometimes in the cervix. These are characterized by a slight amount of stroma, and a predominance of glandular tissue, the cells of which lie in close apposition and are highly differentiated. The second type, the usual form of adenocarcinoma of the fundus, is characterized by areas of apparent duplication of the glands of normal endometrium, while in other areas the true carcinomatous nature of the tumor is evident.

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* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Pathology, 1922. Published in full in Surg., Gynec., and Obstetrics, 1923, xxxvii. From the Section on Surgical Pathology, Mayo Clinic.

The cells in the latter areas have all the morphologic characteristics of carcinoma cells and are arranged in a typical gland formation. There is a moderate amount of stroma between the carcinoma cells. The third group is the papillary adenocarcinoma and in it the connective tissue stroma, as in adenoma malignum, is very sparse and the glandular tissue rests on trabeculæ of thin connective tissue. In a fourth group he places the cases of adenocarcinoma solidum in which are seen only few areas with glandular arrangement and large numbers of closely packed undifferentiated cells. The last group comprises adenocarcinomas showing, in the midst of the cylindrical cell masses, cornified cells and even epithelial pearls, not unlike those found in squamous-cell carcinoma of the cervix.

The carcinomas arising from the surface epithelium show marked variation, are very rare, and are found in older persons. The most interesting type is that which covers the entire mucosa as a squamous-cell carcinoma without glandular formation, which may or may not be cornified. The underlying tissues may be infiltrated with small celled, carcinomatous projections, and the surface may be papillary.

Ewing divides carcinoma of the uterus anatomically into a circumscribed and a diffuse group, and says that the diffuse are probably the advanced stages of the circumscribed. Histologically he follows a classification very similar to that of Kaufmann.

Under the histologic types of carcinoma of the body of the uterus Aschoff describes the adenoma malignum, adenocarcinoma, solid or medullary carcinoma, and the squamous-cell carcinoma, adding that in the same carcinoma one or even all types may be present.

Cullen does not divide carcinoma of the uterus into definite groups. He asserts that while all cases may be grouped under one main heading, the grouping varies greatly in individual cases. He is of the opinion that if the papillary arrangement is the most marked, the origin of the tumor is from the surface epithelium; whereas, when the gland-like arrangement predominates, the process has started first in the glands.

No special attempt has been made to classify anatomically the cases in this series other than to note the general shape, extent of involvement of the uterine cavity, and invasion of the myometrium in relation to the histologic type. From the histologic appearance an attempt has been made to prognosticate the relative degree of malignancy or mortality of a group of cases, taking as a basis the cellular changes. That there are other factors cannot be denied; such as the rate and extent of growth manifested in the amount of uterine cavity involved, the degree of invasion of the myometrium, the late involvement of lymph nodes, and also the uncertain factor, personal resistance to carcinoma. Many of these factors are not recorded. Cellular differentiation alone does not explain the high mortality of certain carcinomas whose cells were well differentiated, or the long duration of postoperative life of other patients whose carcinomas were histologically highly malignant. Taken as a whole, however, cellular differentiation appears to be the most important factor.

Each case of the series was studied separately. MacCarty's standard of cellular differentiation was followed. Cells arranged according to the general direction of adult tissue or with normal polarity, with normal appearance of cytoplasm and nucleoplasm, and with normal function, that is, completely differentiated, are grouped as showing tertiary differentiation, expressed as Differentiation 3. Differentiation 2 consists of the establishment of tissue polarity, but morphologic undifferentiation of cells (Figs. 113 and 114). Primary differentiation consists of morphologic undifferentiation of cells, but alignment according to the general direction of adult tissue (Fig. 115). Thus cells showing no

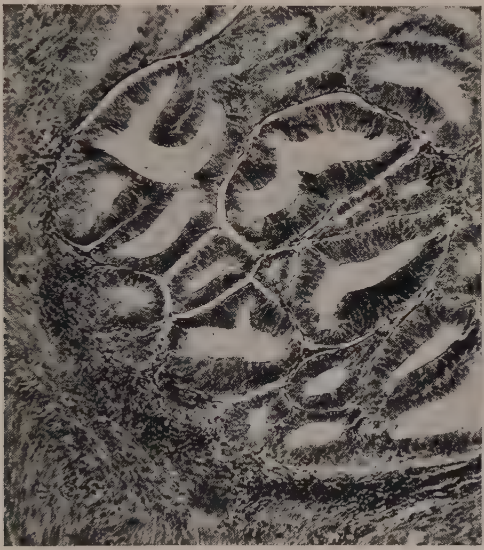

Fig. 113 (Case A146326).—Photomicrograph of adenocarcinoma, Grade 1, showing secondary cellular differentiation.

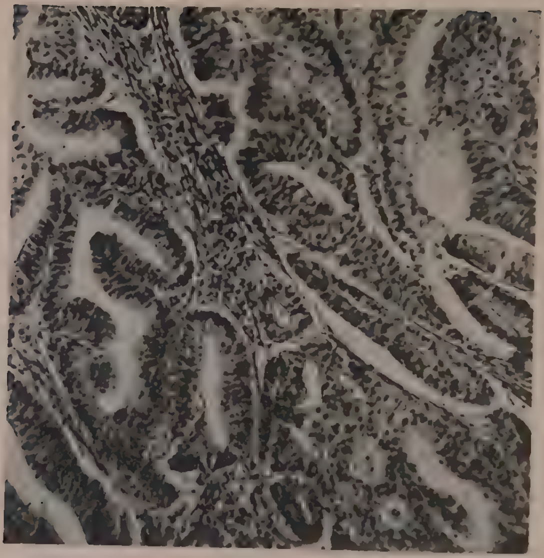

FIG. 114 (Case A59495).—Area of an adenocarcinoma showing secondary cellular differentiation.

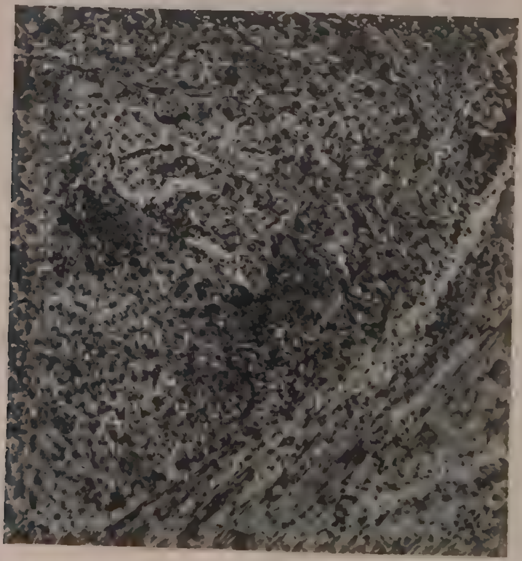

FIG. 115 (Case A124544).—Photomicrograph showing primary cellular differentiation predominating.

differentiation, Differentiation 0, have neither morphologic differentiation nor alignment (Figs. 116 and 117).

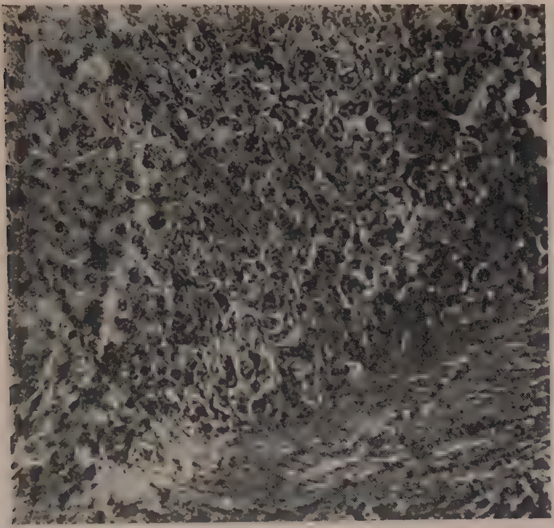

FIG. 116 (Case A190227).—Photomicrograph of an adenocarcinoma, Grade 4.

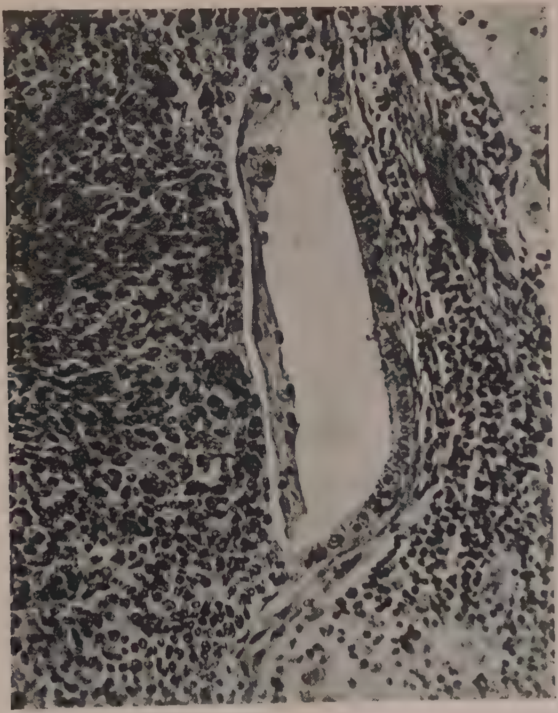

FIG. 117 (Case A274979).—Photomicrograph of an adenocarcinoma whose cells, having no differentiation, completely surround a normal uterine gland.

Appreciating that the degree of malignancy is dependent on the phenomenon of cellular differentiation, the foregoing types were also incorporated into different grades of malignancy, Grades 1, 2, 3, and 4, similar to Broders' classification of squamous-cell epitheliomas (Figs. 113–117). Grade 4 represents highly malignant cases in which the cells show Differentiation 0 throughout practically the entire tumor, although occasional areas may show some primary differentiation (Fig. 117). Grade 3 includes carcinomas showing largely Differentiation 0, some primary differentiation, and occasional areas may show secondary differentiation (Fig. 115). Grade 2 carcinomas show a predominance of secondary differentiation throughout, and occasional areas of primary differentiation (Fig. 114). Grade 1 comprises early cases, in which the carcinoma is extremely small and the cells show high differentiation, secondary throughout (Fig. 113).

The average age of the 186 patients was fifty-five and one-hundredth years, the oldest was seventy-three and the youngest twenty-one (Table 1). This bears out statistical data in the literature with regard to the insignificant mortality from carcinoma of the female genital organs before the age of twenty-five years. Occasional cases of carcinoma of the uterus are cited in the literature in persons younger than twenty years, but the authenticity of most of these is severely questioned. Ganghofner reports a case of cancer of the portio in a girl of eight years. This case, according to Williams, is not a true carcinoma, but a cauliflower excresence of epithelial hyperplasia, although Chiari examined the tumor histologically, and his report should be authentic. Cragin reports a case of carcinoma of the uterus in a girl of eighteen years, on whom a radical abdominal hysterectomy was performed, and recurrence had not taken place during a period of five months. In the series of adenocarcinomas of the uterus collected by Cullen the two youngest patients were thirty years.

The average age of patients in the series at menopause was forty-eight and eight-tenths years, showing that catamenia is relatively not altered in patients with carcinoma of the uterus (Table 1). In comparison to the average age, fifty-five and one-hundredths years, one is led to believe that a certain etiologic relation exists between decline of functional activity and malignant disease, and that the liability to cancer increases as the decline of function progresses. This fact is further emphasized when we compare the active marital lives of these patients, with regard to the number of pregnancies, with otherwise normal patients (Table 1).

TABLE 1

ADENOCARCINOMA OF THE BODY OF THE UTERUS: 186 CASES FROM JANUARY 27, 1905 TO JANUARY 1, 1919

	Years.	Number.	Per cent.
Patients	.....	186	
Age:			
Youngest	21		
Oldest	73		
Average	55.01		
Family history of malignancy	.....	29	15.59
Single	.....	18	9.63
Married	.....	168	90.33
Never pregnant	.....	63	33.87
Total pregnancies	.....	123	66.12
Pregnancies for each married patient	.....	2.4	
Patients having had miscarriage	.....	53	28.49
Total miscarriages	.....	75	
Miscarriages for each married patient	.....	0.43	
Menopause:			
Youngest	35		
Oldest	55		
Average	48.8		

The longest duration of symptoms occurred in cases of Grades 2 and 3; the longest average duration of symptoms was in the least malignant, Grade 1, and the shortest average duration of symptoms in the most malignant, Grade 4 (Table 3). This difference when compared with the extent of involvement of the uterine cavity and the amount of invasion of myometrium (Fig. 118) with regard to the degree of malignancy and cellular differentiation (Tables 6 and 8), illustrates that a tumor of a high degree of malignancy and low cellular differentiation grows larger and invades more extensively in the same period of time, than a tumor of a lower degree of malignancy, and high cellular differentiation. The amount of invasion of the myometrium is designated as Grades 1, 2, 3, and 4; Grade 1 denotes microscopic involvement of the muscle; Grade 2, invasion of one-half of the approximate width of the muscle; Grade 3, invasion to the serosa, and Grade 4, invasion of all the muscle layer and the serosa.

The clinical symptoms (Table 4) illustrate that vaginal discharge, especially if blood tinged, is the most out-standing feature, occurring in 92.46 per cent of all cases. Loss of weight and strength occupy the next place of importance, while odorous discharge except in advanced cases is of relatively little diagnostic value.

Sixty-one and twenty-nine hundredths per cent of the 186 cases are in Grade 2; 29.03 per cent are in Grade 3 (Table 2). In comparison, squamous-cell carcinomas of the cervix, graded similarly by Broders, are more malignant; the larger number of his cases fall into Grades 3 and 4. The number of patients obtaining good postoperative results in Broders' series was 20 per cent, while in this series 61.02 per cent of the patients heard from were still living and the percentage of good postoperative results following vaginal and abdominal hysterectomy was 52.94 per cent and 58.71 per cent respectively. If only the two most malignant grades of carcinoma of the uterus, Grades 3 and 4, are considered, only 35.55 per cent of the patients heard from are living, and good results were obtained in only 32 per cent of the patients operated on. If the larger number of cases of Grade 4 of the squamous-cell carcinomas of the cervix are considered, the difference in percentage of good postoperative results in the two types is further equalized. The differences in life expectancy between the two types of uterine carcinoma and in carcinomas found elsewhere, may possibly be explained by their differences in the degree of malignancy based on the cellular differentiation. Such factors as the lymph drainage, mode and extent of invasion, and rapidity of growth may be secondary to, and perhaps to a degree

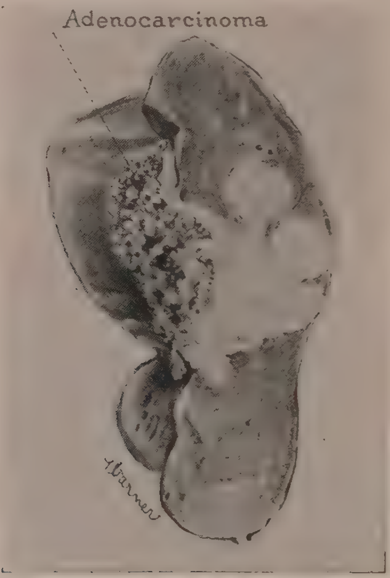

Fig. 118 (Case A91620).—Papillary type of adenocarcinoma of the body of the uterus cut in sagittal section showing extensive invasion of the myometrium.

TABLE 2

Grades of Cellular Differentiation

	Cases.	Per cent.
Grade 1	10	5.37
Grade 2	114	61.29
Grade 3	54	29.03
Grade 4	8	4.30

TABLE 3

Duration of Symptoms According to Grade of Malignancy

	Grade 1, years.	Grade 2, years.	Grade 3, years.	Grade 4, years.	All grades, years.
Longest	4.0	5.0	4.0	3.0	5.0
Shortest	0.08	0.08	2.5	2.5	0.08
Average	1.57	1.25	1.42	1.0	1.29

TABLE 4

Symptoms

	Cases.	Per cent.
Vaginal discharge	182	98.38
Bloody vaginal discharge	172	92.46
Odorous vaginal discharge	53	28.49
Tissue passed	2	1.07
Weight loss (average 20.29 pounds)	44	23.65
Loss of weight and strength (amount not stated)	64	34.40

dependent on, cellular differentiation, and in reality of little real importance with regard to the potential malignancy of the carcinoma.

Taussig found that of forty-five cases of carcinoma of the fundus of the uterus, ten (25 per cent) were associated with fibromyomas. The percentage in this series is somewhat higher for the reason that they include even the most minute intramural fibromyoma (Table 5). That this is a factor in the etiology of carcinoma can hardly be accepted when compared with the number of fibromyomas found in non-malignant uteri at hysterectomy and the overwhelming number of fibromyomatous uteri compared with carcinomatous uteri.

TABLE 5

Associated Fibromyomas, Fifty-seven Cases

	Cases.	Per cent.
Grade 1	5	55.55 of 9
Grade 2	30	30.30 of 99
Grade 3	19	42.22 of 45
Grade 4	3	37.5 of 8
Total	57*	35.4 of 161

* Only this number was available for this study.

TABLE 6

Relation of Various Factors to Grade of Malignancy

Extent of Involvement of Uterine Cavity, Expressed in Fifths

Involvement.	Cases.	Grade 1. Per cent.	Cases.	Grade 2. Per cent.	Cases.	Grade 3. Per cent.	Cases.	Grade 4. Per cent	Cases.	All grades. Per cent.
1/5	4	44.44 of 9	17	17.00 of 100	4	8.88 of 48	..	....	25	15.53 of 162*
2/5	3	33.33 of 9	13	13.00 of 100	4	8.88 of 48	1	12.50 of 8	21	12.96 of 162
3/5	..	....	12	12.00 of 100	9	20.00 of 48	1	12.50 of 8	22	13.58 of 162
4/5	2	22.22 of 9	34	34.00 of 100	15	33.33 of 48	1	12.50 of 8	52	32.09 of 162
5/5	..	....	24	24.00 of 100	13	28.88 of 48	5	62.50 of 8	42	25.93 of 162
					Invasion of Myometrium					
Grade.										
1	6	66.66 of 9	27	27.27 of 99	7	15.55 of 45	1	12.50 of 8	41	25.46 of 161*
2	3	33.33 of 9	36	36.36 of 99	16	35.55 of 45	3	37.50 of 8	56	34.78 of 161
3	..	....	23	23.23 of 99	10	22.22 of 45	..	....	35	21.73 of 161
4	..	....	13	13.13 of 99	12	26.66 of 45	4	50.00 of 8	29	18.01 of 161
					Shape of Lesion					
Papillary	4	44.44 of 9	78	78.78 of 99	31	68.88 of 45	4	50.00 of 8	118	73.29 of 161*
Diffuse	1	11.11 of 9	12	12.12 of 99	10	22.22 of 45	2	25.00 of 8	25	15.52 of 161
Polypoid	4	44.44 of 9	9	9.09 of 99	4	8.88 of 45	2	25.00 of 8	18	11.18 of 161
					Lymphocytic Reaction					
Grade.										
1	7	70.00 of 10	45	39.50 of 114	23	42.59 of 54	3	37.50 of 8	78	41.93 of 186
2	3	30.00 of 10	47	41.22 of 114	21	38.88 of 54	2	25.00 of 8	73	39.24 of 186
3	..	....	20	17.62 of 114	10	18.51 of 54	3	37.50 of 8	33	17.74 of 186
4	..	....	2	1.75 of 114	..	....	..	....	2	1.07 of 186
					Cellular Differentiation					
Differentiation.										
0	..	....	..	....	..	....	3	37.50 of 8	3	1.61 of 186
1	..	....	2	1.75 of 114	30	55.55 of 54	5	62.50 of 8	37	19.87 of 186
2	..	....	112	98.24 of 114	24	44.44 of 54	..	....	146	78.49 of 186

* Only this number (of 186 cases) were available for this study.

The shapes of the lesions (Tables 6 and 8) to a certain extent appear to be dependent on cellular differentiation. The carcinomas in the least malignant group and those showing the greatest differentiation were largely papillary or polypoid in shape (Figs. 119, 120, 121), while the most malignant and those showing the least cellular differentiation were those designated as the diffuse or flat type (Fig. 122), as distinguished from the papillary or polypoid types which are raised above the surface of the uterine mucosa. In carcinomas of the bladder, those of the papillary type are less malignant than the flat type.[10] However, other factors, such as mechanical pressure, play a part in determining shape, especially in tumors growing in cavities. Likewise polypoid tumors are surface tumors arising from a local hyperplasia which tends to be non-invasive.

TABLE 7

CELLULAR DIFFERENTIATION OF 186 CASES

	Cases.	Per cent.
Differentiation 0	3	1.61
Differentiation 1	37	19.89
Differentiation 2	146	78.49

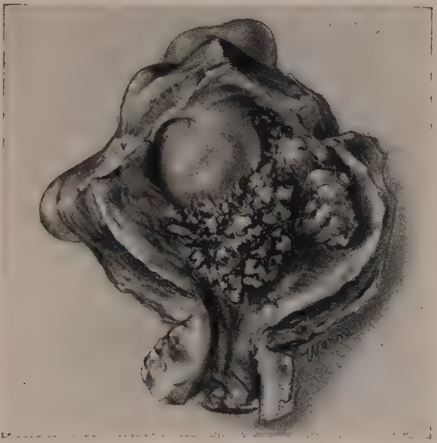

FIG. 119 (Case A146326).—Papillary type of adenocarcinoma of the body of the uterus associated with fibromyomas.

In the general ultimate results according to the four grades of malignancy (Table 8) all patients with Grade 1 malignancy are still living, while those with Grade 4 malignancy are dead. Referring to

TABLE 8

Relation of Various Factors to Cellular Differentiation

Extent of Involvement of Uterine Cavity, Expressed in Fifths

	Differentiation 0.		Differentiation 1.		Differentiation 2.		Total.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
1/5	..	....	2	6.66 of 30	22	17.18 of 128	24	14.90 of 161*
2/5	..	....	5	16.66 of 30	17	13.28 of 128	22	13.66 of 161
3/5	..	....	7	23.33 of 30	16	12.50 of 128	23	14.28 of 161
4/5	..	....	7	23.33 of 30	45	35.15 of 128	52	32.29 of 161
5/5	3	100 of 3	9	30.00 of 30	28	21.87 of 128	40	24.84 of 161
				Invasion of Myometrium				
Grade.								
1	..	....	5	16.66 of 30	36	28.12 of 128	41	25.46 of 161*
2	1	33.33 of 3	11	36.66 of 30	46	35.93 of 128	58	36.02 of 161
3	..	....	6	20.00 of 30	27	21.09 of 128	33	20.49 of 161
4	2	66.66 of 3	8	26.66 of 30	19	14.84 of 128	29	18.01 of 161
				Shape of Lesion				
Papillary	1	33.33 of 3	16	53.33 of 30	101	78.90 of 128	118	73.29 of 161*
Diffuse	2	66.66 of 3	8	26.66 of 30	15	11.71 of 128	25	15.52 of 161
Polypoid	..	....	6	20.00 of 30	12	9.37 of 128	18	11.18 of 161
				Lymphocytic Reaction				
Grade.								
1	1	33.33 of 3	14	37.83 of 37	63	43.15 of 146	78	41.93 of 186
2	1	33.33 of 3	14	37.83 of 37	58	39.72 of 146	73	39.24 of 186
3	1	33.33 of 3	8	21.62 of 37	24	16.43 of 146	33	17.74 of 186
4	..	....	1	2.70 of 37	1	0.68 of 146	2	1.07 of 186

* Only 161 cases were available for this study.

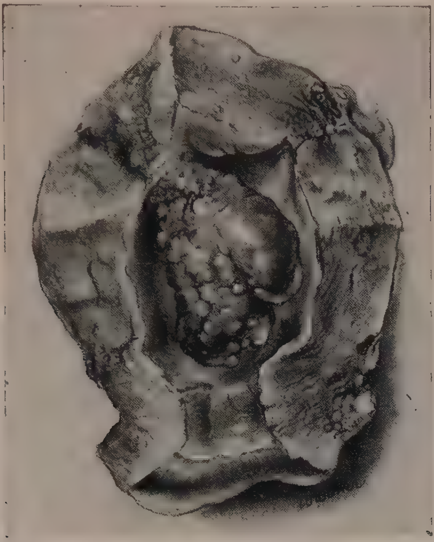

Fig. 120 (Case A341145).—Polypoid type of adenocarcinoma of the body of the uterus originating in the right horn.

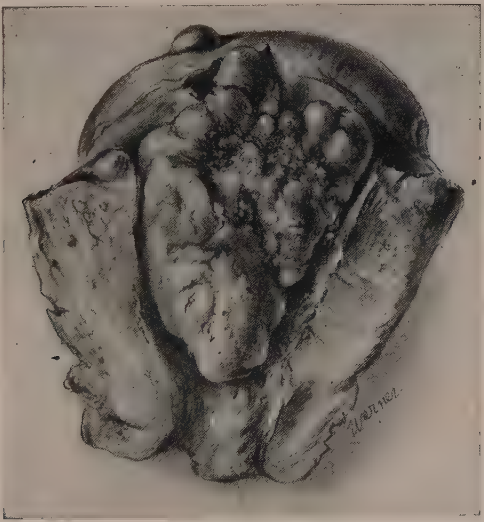

Fig. 121 (Case A145635).—Polypoid type of adenocarcinoma of the body of the uterus of high degree of malignancy.

the cause of death of these patients (Table 12) 75 per cent died of carcinoma. Of patients with Grade 2 malignancy, 71.76 per cent are still alive, while in Grade 3 only 38.09 per cent are alive. The cause of death due to carcinoma in these two groups is 62.06 per cent and 74.19 per cent respectively. Thus not only the number of patients dead increases as the degree of malignancy increases, but the number of deaths due to carcinoma increases.

These facts are likewise verified in a consideration of the ultimate results of the cases grouped on a basis of cellular differentiation. The highest, Differentiation 2, showed the largest percentage of living patients (65.78 per cent) and the smallest number dead (34.21 per cent); while the next group showing primary differentiation as the highest degree of cellular differentiation had the smallest number of living patients (36.36 per cent) and the largest number dead (63.63 per cent) (Table 12). The average duration of symptoms and the average length of postoperative life are somewhat longer in the group showing the highest cellular differentiation.

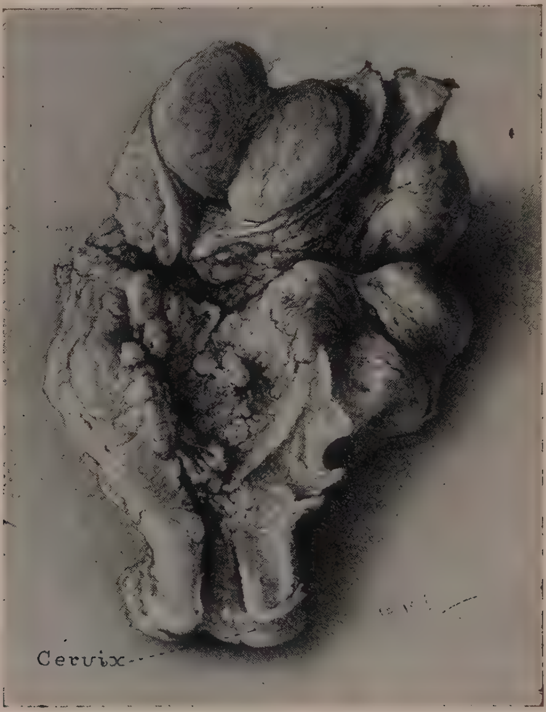

FIG. 122 (Case A335600).—Diffuse type of adenocarcinoma of the body of the uterus associated with fibromyomas.

Abdominal hysterectomy was performed on 136 (73.11 per cent) of the 186 patients, while forty-five (24.19 per cent) had vaginal hysterectomies (Table 10). More than one-half of the patients who were thus treated had good results, and are living, or death has resulted from some cause other than carcinoma. The good results in both vaginal and abdominal hysterectomy decrease in percentage as the degree of malignancy increases. With this decrease in percentage of living patients with good results there is a corresponding increase in deaths from operation and recurrence.

It is of interest that in this series vaginal hysterectomy shows a slight increase in the percentage of recurrence both in the number of living patients with recurrence and in the percentage of carcinoma deaths (Table 12). Operative death rate is slightly higher in cases in which abdominal hysterectomies have been performed while the percentage of good postoperative results is somewhat higher than in vaginal hysterectomy.

The classification of cases according to the highest cellular differentiation found throughout the carcinomas, and the grouping according to grades show no difference in the total ultimate results. The latter grouping perhaps gives the pathologist a somewhat larger scope. However, the foregoing facts demonstrate that the postoperative prognosis of a group of patients with adenocarcinoma can be determined by a close study of the cellular differentiation of the carcinoma.

CONCLUSIONS

1. The mortality and frequency of carcinoma of the body of the uterus rank within the first two places in carcinoma in the female. Such carcinoma is extremely rare before the age of twenty-five years.
2. Carcinoma of the body of the uterus is found in about 30 per cent of all uterine carcinomas.
3. Apparently a definite relation exists between the decline of functional activity and malignant disease of the body of the uterus.
4. The more active the carcinoma, the shorter the clinical symptoms.
5. Vaginal discharge, especially if blood tinged, is the most outstanding clinical feature of carcinoma of the uterus.
6. The accepted belief of a relatively favorable outlook for carcinoma of the body of the uterus in comparison to carcinoma of the cervix has a pathologic basis in that the number of cases which show a high degree of differentiation are in the majority, and the more malignant types are rare.

TABLE 9

Clinical Diagnoses in 186 Cases of Carcinoma of Body of Uterus

	Cases.	Per cent.
Definite	75	40.32
Questionable	36	19.35
Diagnosed other than carcinoma of uterus	68	36.55
Diagnosis not recorded	7	3.76

TABLE 10

Surgical Treatment

	Cases.	Per cent.
Total abdominal hysterectomy with removal of tubes and ovaries	128	68.81
Subtotal abdominal hysterectomy with removal of tubes and ovaries	8	4.30
Vaginal hysterectomy with removal of tubes and ovaries	7	3.76
Vaginal hysterectomy	38	20.43
Curettage	4	2.14
Cautery	1	0.53

TABLE 11

Cause of Death of Patients Who Died at the Clinic

	Cases.	Per cent.
Peritonitis	5	2.68
Myocardial degeneration	2	1.07
*Pneumonia	1	0.53
Intestinal obstruction	2	1.07
Pulmonary embolism	1	0.53
Operative mortality	11	5.91

* One death from pneumonia followed thyroidectomy one year after hysterectomy for carcinoma of the uterus.

TABLE 12

GENERAL ULTIMATE RESULTS

According to Degree of Malignancy

Patients traced.... 136 (73.11 per cent of 186)

	Grade 1.		Grade 2.		Grade 3.		Grade 4.		All grades.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Patients living	6	100 of 6	61	71.76 of 85	16	38.09 of 42	..	....	83	61.02 of 136
Postoperative life	..	Years	..	Years	..	Years	..	....	..	Years
Longest	..	2.18	..	15.63	..	14.39	..	....	..	15.63
Shortest	..	3.51	..	3.005	..	3.35	..	....	..	3.005
Average	..	7.24	..	7.27	..	7.05	..	....	..	7.23
Patients dead (cause other than operation)	..	....	24	28.23 of 85	26	61.90 of 42	3	100 of 3	53	38.97 of 136
Postoperative life	..	....	..	Years	..	Years	..	Years	..	Years
Longest	..	....	..	10.76	..	13.66	..	1.23	..	13.66
Shortest	..	....	..	0.33	..	0.106	..	0.082	..	0.082
Average	..	....	..	2.96	..	1.91	..	0.759	..	2.29

According to Cellular Differentiation

	Differentiation 0.		Differentiation 1.		Differentiation 2.		Total.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Patients living	..	....	8	36.36 of 22	75	65.78 of 114	83	61.02 of 136
Postoperative life	..	....	..	Years	..	Years	..	Years
Longest	..	....	..	11.51	..	15.66	..	15.66
Shortest	..	....	..	4.35	..	3.005	..	3.005
Average	..	....	..	6.51	..	7.30	..	7.23
Patients dead (cause other than operation)	..	....	14	63.63 of 22	39	34.21 of 114	53	38.97 of 136
Postoperative life	..	....	..	Years	..	Years	..	Years
Longest	..	....	..	13.66	..	10.76	..	13.66
Shortest	..	....	..	0.106	..	0.106	..	0.106
Average	..	....	..	0.027	..	2.36	..	2.27

TABLE 12—*Continued*

*Cause of Death**

	Grade 1.		Grade 2.		Grade 3.		Grade 4.		All grades.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Carcinoma	..	....	18	62.06 of 29	23	74.19 of 31	3	75.00 of 4	44	67.69 of 65
Carcinoma (?)	..	....	1	3.44 of 29	1	3.22 of 31	..	....	2	3.07 of 65
Operation	1	100 of 1	4	13.79 of 29	5	16.12 of 31	1	25.00 of 4	11	16.91 of 65
Other than carcinoma	..	....	4	13.79 of 29	1	3.22 of 31	..	....	5	7.69 of 65
Unknown	..	....	2	6.89 of 29	1	3.22 of 31	..	....	3	4.61 of 65
Total	..	....	..	....	..	....	..	....	65	43.91 of 148
Patients Who Had Abdominal Hysterectomies (136 Cases)										
Patients from whom information was received	..	....	..	....	..	....	..	....	109	80.14 of 136
Patients from whom information was not received	..	....	..	....	..	....	..	....	27	19.85 of 136
Living:										
Good results	3	75.00 of 4	46	65.64 of 68	12	35.29 of 34	..	....	61	55.96 of 109
Recurrence	..	....	1	1.47 of 68	..	....	..	....	1	0.91 of 109
Patients dead:										
From operation	1	25.00 of 4	3	4.41 of 68	4	11.76 of 34	1	33.33 of 3	9	8.25 of 109
Other causes	..	....	3	4.41 of 68	..	....	..	....	3	2.75 of 109
Carcinoma	..	....	13	19.11 of 68	16	47.05 of 34	2	66.66 of 3	31	28.44 of 109
Unknown	..	....	2	2.94 of 68	2	5.88 of 34	..	....	4	3.66 of 109
Patients Who Had Vaginal Hysterectomies (Forty-five Cases)										
Patients from whom information was received	..	....	..	....	..	....	..	....	34	75.56 of 45
Patients from whom information was not received	..	....	..	....	..	....	..	....	11	24.44 of 45
Living:										
Good results	1	100 of 1	13	65.00 of 20	3	25.00 of 12	..	....	17	50.00 of 34
Recurrence	..	....	1	5.00 of 20	..	....	..	....	1	2.94 of 34
Patients dead:										
From operation	..	....	1	5.00 of 20	1	8.33 of 12	..	....	2	5.88 of 34
Other causes	..	....	..	....	1	8.33 of 12	..	....	1	2.94 of 34
Carcinoma	..	....	4	20.00 of 20	7	58.33 of 12	1	100 of 1	12	35.29 of 34
Unknown	..	....	1	5.00 of 20	..	....	..	....	1	2.94 of 34

* Information received from relative, home physician, or other reliable source.

TABLE 12—*Continued*

Patients Who Had Abdominal Hysterectomies (136 Cases)

	Differentiation 0.		Differentiation 1.		Differentiation 2.		Total.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Patients from whom information was received	..	....	..	....	..	....	109	80.14 of 136
Patients from whom information was not received	..	....	..	....	..	....	27	19.85 of 136
Living:								
Good result	..	....	5	25.00 of 20	56	63.63 of 88	61	55.96 of 109
Recurrence	..	....	..	....	1	1.13 of 88	1	0.91 of 109
Patients dead:								
From operation	1	100 of 1	4	20.00 of 20	4	4.54 of 88	9	8.25 of 109
Other causes	..	....	..	....	3	3.40 of 88	3	2.75 of 109
Carcinoma	..	....	9	45.00 of 20	22	25.00 of 88	31	28.44 of 109
Unknown	..	....	2	10.00 of 20	2	2.27 of 88	4	3.66 of 109

Patients Who Had Vaginal Hysterectomies (Forty-five Cases)

	Differentiation 0.		Differentiation 1.		Differentiation 2.		Total.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Patients from whom information was received	..	....	..	....	..	....	34	75.56 of 45
Patients from whom information was not received	..	....	..	....	..	....	11	24.44 of 45
Living:								
Good result	..	....	2	33.33 of 6	15	53.57 of 28	17	50.00 of 34
Recurrence	..	....	..	....	1	3.57 of 28	1	2.94 of 34
Patients dead:								
From operation	..	....	1	16.66 of 6	1	3.57 of 28	2	5.88 of 34
Other causes	..	....	1	16.66 of 6	..	....	1	2.94 of 34
Carcinoma	..	....	2	33.33 of 6	10	35.71 of 28	12	35.29 of 34
Unknown	..	....	..	....	1	3.57 of 28	1	2.94 of 34

7. Association of fibromyomas with carcinoma of the uterus does not appear to play an important part in the etiology.

8. The shape of the lesion appears to be related to the degree of cellular differentiation, for the more malignant the carcinoma, the less liable it is to assume a papillary form.

9. A carcinoma of a high grade of malignancy grows larger and invades more extensively in a given length of time, than one of a lower degree of malignancy. Lymphocytic reaction appears more marked in groups showing a higher degree of malignancy.

10. The clinical diagnosis of carcinoma of the body of the uterus, before curettage or hysterectomy, is possible in 40 per cent of all cases.

11. The longest length of life since operation of those patients who are now dead occurred in cases of Grade 2 malignancy, while the shortest occurred in Grade 4. The greatest average length of life since operation of those patients who are now living occurred in cases of Grade 2 malignancy, and the shortest in Grade 3. None of the patients with Grade 4 malignancy is now living.

12. The shortest length of life since operation of those patients who are now dead occurred in Grade 4 and the longest in Grade 2.

13. The shortest average length of life following operation of patients who are now dead occurred in Grade 4 and the longest in Grade 2. Grade 1 contained no patients who are now dead.

14. Grade 1 contains the largest percentage of living patients and Grade 4 contains none, while Grades 2 and 3 contain 71.76 per cent and 38.09 per cent respectively.

15. The largest percentage of deaths from carcinoma occurs in Grade 4 and a smaller percentage in each group to Grade 1, in which there have been no deaths from carcinoma.

16. Abdominal hysterectomy in this series of cases was performed more often than vaginal hysterectomy and the incidence of postoperative good results among living patients is slightly higher among those having abdominal hysterectomy. The percentage of recurrence is slightly higher in vaginal hysterectomy.

17. The sum total of ultimate results shows practically no variation when interpreted from a basis of relative amount of a definite type of cellular differentiation present in the tumor expressed in Grades 1 to 4, than when the interpretation depends on the highest type of differentiation present in the tissue.

18. A series of adenocarcinomas of the uterus can be so classified

according to groups, expressing various degrees of malignancy, that the ultimate postoperative results obtained will vary in direct proportion to the mortality of each group.

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III

DUCTLESS GLANDS

THE BLOOD SUPPLY OF THE THYROID GLAND AND ITS SURGICAL SIGNIFICANCE*

EDWARD V. MASTIN

In order to ascertain to what extent the blood supply of the thyroid gland is affected by ligations, I deemed it advisable to study the various possible anastomoses. A detailed study of the blood supply was made by injecting the blood vessels of twenty-five necropsy specimens (after the method of Gross) with a barium-carmin-gelatin mixture, which was heated on a water bath to a temperature of about 60° C. The injections were made with a 10 c.c. syringe under enough pressure to fill the capillaries. While the inferior thyroid artery was being injected, the solution ran out of the superior thyroid of the same side in all of the cases, out of the superior thyroid of the opposite side in 30 per cent of the cases, and out of the superior thyroids of both sides and the opposite inferior thyroid in 20 per cent. When the primary injection into the superior thyroid artery was made, the injected material could be seen in the inferior thyroid of the same side in all cases, in the superior thyroid of the opposite side in 80 per cent of the cases, and in all the vessels in 20 per cent of the cases. Various combinations of injections were used and roentgenograms were made after each injection. Later, the specimens were fixed in kaiserling and dissected. The best results were obtained by studying normal thyroids or small colloid goiters. The exophthalmic goiters were difficult to inject and the vessels did not show up well.

The principal arterial trunks ramified on the surface of the gland within the true capsule and anastomosed freely with one another. Anastomosis was freer between the various vessels of the same side than between those of opposite sides, although there was a well marked branch of communication through the isthmus.

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* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, 1922. Published in Surgery, Gynecology, and Obstetrics, 1923, xxxvi, 69–74. From the Section on Surgery, Mayo Clinic.

The larger arteries were distributed principally over the surface of the gland; there was only an occasional large vessel deep in the parenchyma. Each artery gave off several branches, some of which supplied the anterior surface of the gland and some the posterior. The main continuations of these arteries most commonly ran along and on the margins of the gland (Figs. 123 and 124).

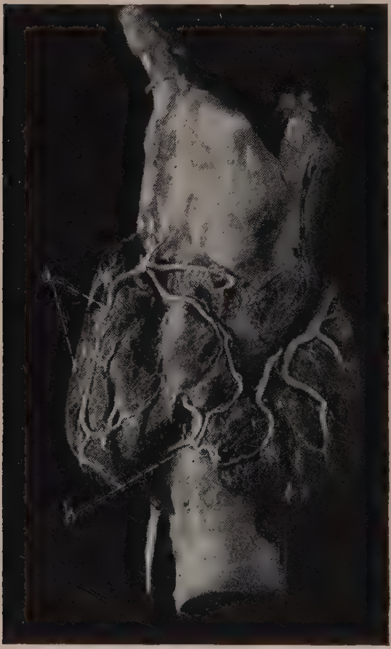

Fig. 123.—Anterior view of a dissected thyroid gland injected with a carmin-gelatin-bismuth preparation showing: a, Longitudinal anastomosis between inferior and superior thyroid arteries of the left side, and b, complex anastomosis between both superior thyroid arteries and the inferior thyroid artery of the left side.

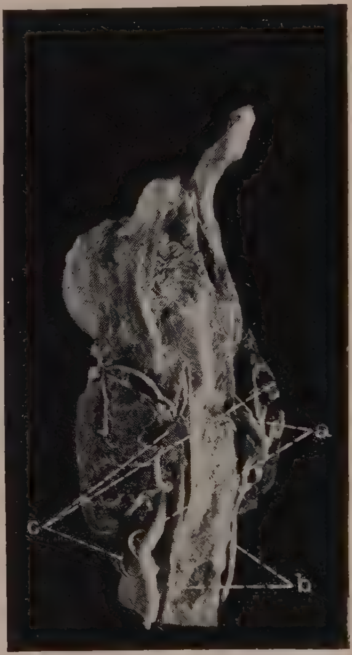

Fig. 124.—Posterolateral view of a dissected thyroid injected with a carmin-gelatin-bismuth preparation: a: Blood vessel; b, recurrent laryngeal nerves; and c, parathyroids.

The superior thyroid artery was more constant in division and distribution than the inferior thyroid artery. It generally divided into three branches. The largest branch ran downward over the anterior surface of the gland, sending branches in all directions; some of these ramified over the surface of the gland, some supplied the parenchyma of the gland, others anastomosed with the superior thyroid of the opposite side, and still others, with the inferior of the same side. The next largest branch descended along the posterior border of the gland and anastomosed with the inferior thyroid, sending branches to the parenchyma of the gland and to the trachea. Often a common trunk was formed by this anastomosis, and gave off a terminal artery which supplied the superior parathyroid body. The third branch entered the substance of the gland and with the other parenchymal branches, as shown by Major, rapidly divided and formed a network of vessels supplying the lobules (Fig. 125).

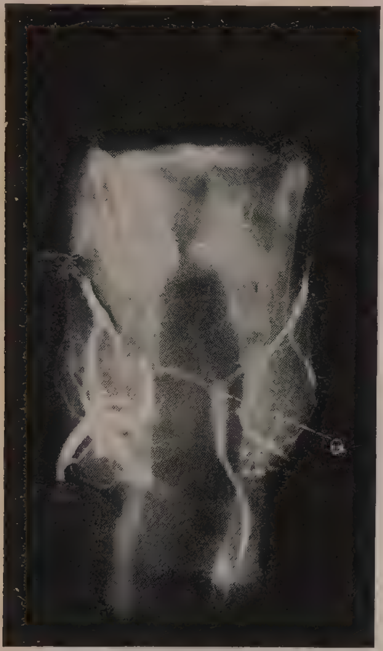

Fig. 125.—Roentgenogram of normal thyroid after injection of all four thyroid vessels with a carmin-gelatin-bismuth preparation showing complex anastomosis at isthmus at *a*.

The inferior thyroid artery divided into two or more branches at varying distances from the gland. Latarjet and Alamartine report instances in which the division occurred quite close to the thyroid axis, and one case in which was a double inferior thyroid artery. Dwight reports an absence of the inferior thyroid artery on the right in one case and on the left in five cases in a series of 437. The principal branches of this artery entered the capsule of the gland on the posterior surface in the neighborhood of the middle third. A few of these branches ramified over the surface of the gland, while one large branch ran along the inferior border toward the isthmus. The number of branches and the points at which they enter the gland may vary considerably. In the cases studied, the average point at which the principal branch of the inferior thyroid artery entered the capsule of the gland was 4.5 cm. from the superior pole, and 1.8 cm. from the inferior pole; the length of the lobe averaged 6.34 cm. In one case the uppermost branch entered the capsule 1 cm. from the superior pole. In another case the lowest branch entered the capsule 0.25 cm. from the inferior pole. The inferior thyroid artery was about one-third larger than the superior thyroid artery. The average inferior thyroid vessel measured 2.78 mm.; the average superior thyroid artery measured 1.87 mm.; the largest inferior was 3.68 mm.; the smallest was 1.90 mm. The largest superior thyroid artery measured 2.38 mm., and the smallest 1.57 mm. In some instances definite arteries ran through the tracheal rings and entered the posterior surface of the gland; in others branches from the inferior thyroid left the substance of the gland and entered the trachea of its anterolateral surface.

The microscopic blood vessels supplying the thyroid tissue were usually plentiful. The interlobular arteries, which are branches of the parenchymal vessels, were usually two to five in number and broke up into close networks that surrounded the follicles and lay immediately beneath the epithelium (Figs. 126, 127, 128 and 129).

Berard and Destol showed that the anastomoses were on the surface of the gland, and that few, if any, were intraglandular. Latarjet and Alamartine came to similar conclusions in their experiments. The most important anastomosis found in my experiments was the unilateral longitudinal anastomosis between the superior and inferior arteries of the same side. This anastomosis occurred on the lateral and posterior surfaces and occasionally just within the substance of the gland. Of these, the one on the lateral surface was seen most often. One of the branches that united the inferior and superior thyroid arteries most constantly, lay in the angle formed by the trachea and esophagus, and extended along the posterior border of the gland (Fig. 130).

The bilateral anastomoses were, as a rule, less developed, more complex, and extremely varied. Often there was direct communication between the superior thyroid vessels across the upper border of the isthmus, generally anteriorly, but at times posteriorly. Landström and Stricheicen have shown very clearly that such anastomoses are present on the surface of the gland, not only between the arteries of the same side, but also between those of opposite sides. Delore and Alamartine reached similar conclusions in a large series of injections.

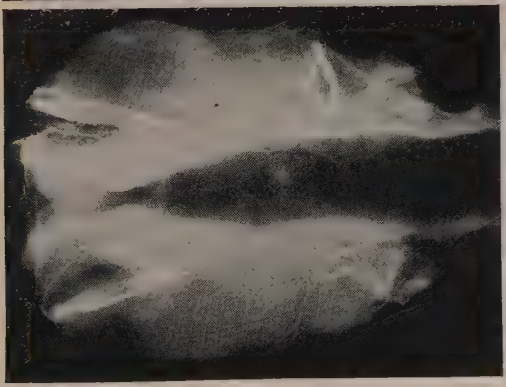

Fig. 126.

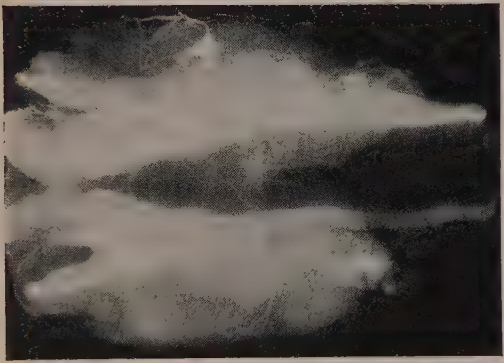

Fig. 127.

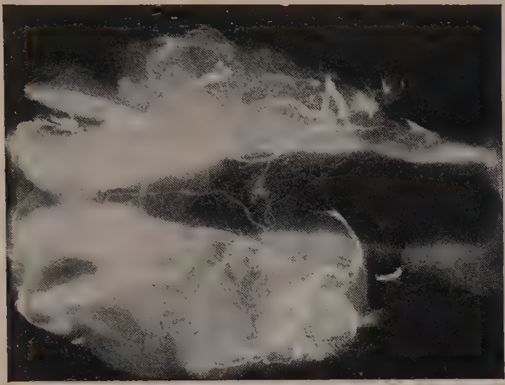

Fig. 128.

Fig. 126.—Result of injection of the right inferior thyroid artery with a carmin-gelatin-bismuth preparation.

Fig. 127.—Result of injection of the right inferior and the right superior thyroid arteries with a carmin-gelatin-bismuth preparation.

Fig. 128.—Result of injection of the right superior thyroid artery and both inferior thyroid arteries with a carmin-gelatin-bismuth preparation.

In this study no direct anastomosis was noted between the two inferior thyroid arteries (Fig. 131).

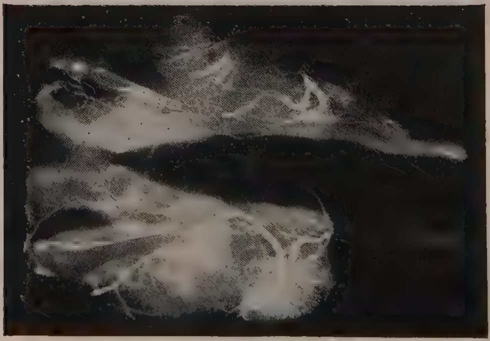

Fig. 129.

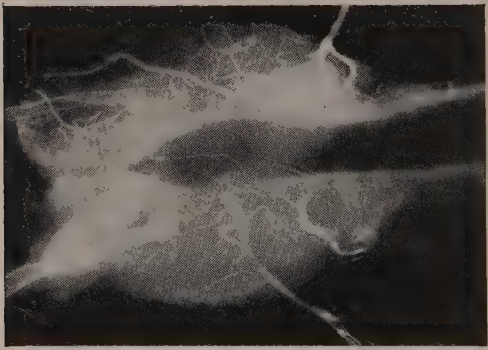

Fig. 130.

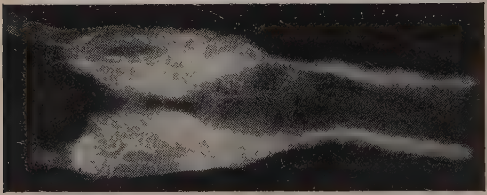

Fig. 131.

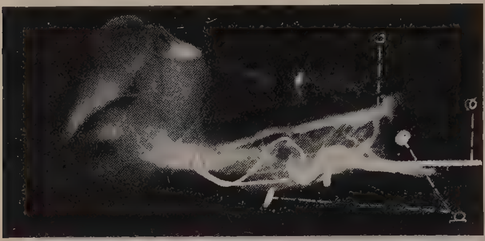

Fig. 132.

Fig. 129.—Result of injection of all four thyroid arteries with a carmin-gelatin-bismuth preparation.

Fig. 130.—Result of injection of right inferior thyroid artery with a carmin-gelatin-bismuth preparation, showing a very extensive anastomosis.

Fig. 131.—Roentgenogram of trachea after all thyroid vessels had been injected with a carmin-gelatin-bismuth preparation.

Fig. 132.—Roentgenogram showing relation of *a*, the recurrent laryngeal nerve, and *b*, the parathyroids, to *c*, the blood supply of the thyroid. Lateral view of a thyroid cut in two. Wire was laid along the nerve and metal tags were placed over the parathyroids.

There is an indirect anastomosis by way of the larynx, trachea, and esophagus, by which the blood supply to the thyroid gland could be reëstablished after ligation of all four arteries. The larynx was supplied by the superior laryngeal and cricothyroid arteries which are branches of the superior thyroid artery, and by the inferior laryngeal artery, a branch of the inferior thyroid. The trachea obtained its blood supply from branches of the inferior laryngeal and inferior thyroid arteries, which anastomosed below with bronchial arteries and with the internal mammary arteries through the anterior mediastinal twigs. Branches of the inferior thyroid artery supplied the esophagus and anastomosed with the lower branches of the ascending pharyngeal artery (Fig. 132).

As a rule, the arteries in the substance of the thyroid gland were accompanied by two veins which were joined at various places by bar-like connections which crossed the arteries. The veins arose from the far side of the capillary network, followed the course of the arteries fairly closely, and anastomosed in a similar manner. They emptied at various places into the larger veins that emerged from the interior of the gland and anastomosed freely on the surface.

On examining the cut surface of injected glands it was observed that the individual vessels were larger in cases of colloid goiters than in cases of exophthalmic, and that the farther away from the capsule the sections were taken, the smaller the vessels. No one questions the vascularity of an active exophthalmic goiter. This seeming contradiction is explained, therefore, by the fact that the lobules and follicles in the exophthalmic goiter are smaller but much more numerous within a given area and, as each has its individual blood supply, the vessels must, of necessity, break up into numerous smaller arterioles and capillaries in order to supply their lobules. In a colloid goiter the vessels in the parenchyma are larger and do not break down into so many minute capillaries as they do in exophthalmic goiter. The colloid is not distributed uniformly throughout the gland, but is in excess and under considerable pressure in various areas. The intralobular vessels are pressed on by this colloid to such extent that the lumina of the vessels are entirely obliterated and the injected material is unable to penetrate them. This observation has been proved histologically by Wilson.

It is not understood just why patients with exophthalmic goiter are benefited by ligation of the superior thyroid arteries. If ligation should completely exclude the blood from the area supplied by the ligated vessel, necrosis would result. We know that it does not, for experiments show that the anastomosis is so rich that circulation can be reëstablished in a short time. Recently, thyroidectomy was performed at the Mayo Clinic about two weeks after all four vessels had been ligated, and little or no difference was noted in the vascularity of the gland (Figs. 133 and 134).

It would appear that some factor other than the blood supply must be responsible for the improvement after ligation. In experiments by Cannon, Binger, and Fitz unmistakable signs of hyperthyroidism were produced in cats by anastomosing the vagus trunk into the superior cervical sympathetic. We can well assume, therefore,

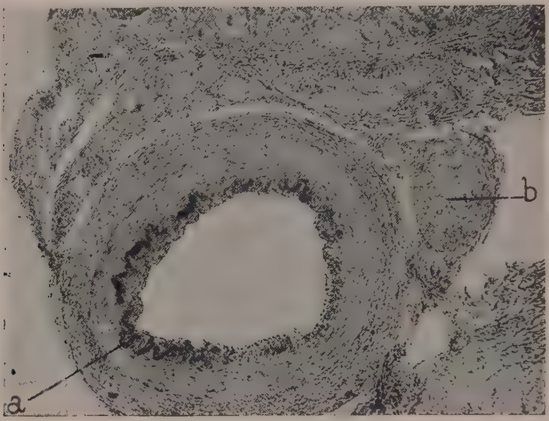

Fig. 133.—Section from a normal thyroid showing *a*, the superior thyroid artery, and *b*, the accompanying nerves. (×40.)

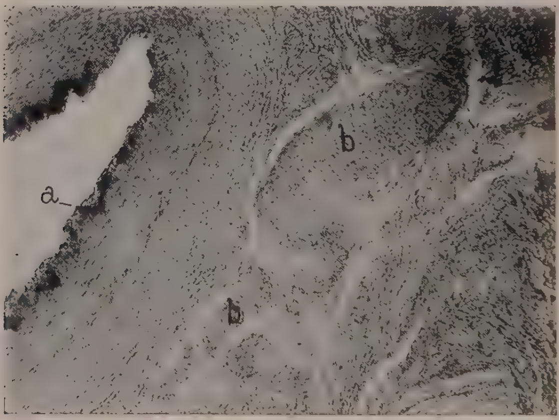

Fig. 134.—Section from an exophthalmic goiter showing *a*, superior thyroid artery, and *b*, large amount of nerve tissue surrounding the artery. (×50.)

that the functional activity of the thyroid is controlled by sympathetic fibers. Ligation of the superior thyroid poles brings about an interruption of the impulses reaching the gland from the superior cervical sympathetic ganglion, since the branches from this ganglion reach the gland in company with the superior thyroid artery, and are ligated with the vessels. Thirty specimens, including segments of the superior thyroid artery and vein, removed during ligation and from necropsy specimens were studied microscopically. Many small nerve bundles were seen to be closely associated with the vessels; others were embedded in the connective tissue. In several gross specimens a small nerve was dissected out and found to follow the course of the superior thyroid artery; it gave off minute branches and entered the gland with the artery. A few microscopic branches which are not closely associated with the superior thyroid artery are found in the loose connective tissue at the superior pole; these enter the gland independently of any vessels.

It would appear that in order to get the maximal benefit from ligations of the superior vessels, a polar ligation should be made in addition to dividing and ligating the superior thyroid artery; this would catch the veins, lymphatics, and remaining nerve filaments. Polar ligations alone do not suffice, for there is no constant point where the superior thyroid artery enters the gland. We have seen patients in whom the superior pole has been ligated, but the artery missed. Pemberton has seen patients whose superior thyroid arteries did not enter the superior pole, but passed directly to the isthmus. In one specimen examined, the principal branch of the superior thyroid passed directly to the isthmus, anastomosing with a branch from the opposite superior.

The improvement which follows superior ligations is not seen following inferior ligations in spite of the fact that the inferior thyroid artery supplies a much larger area than the superior. This may be explained by the fact that there are only a few microscopic nerve filaments accompanying the inferior thyroid vessels. Another factor that may be of importance, if we assume that the activating material passes from the gland by way of its lymphatics, is that the superior lymphatics leave the gland in company with the superior artery and veins, and are ligated at the same time; whereas no veins or lymphatics accompany the inferior thyroid arteries.

Plummer has noted a drop in the basal metabolic rate in patients who have passed through recent crises, some intercurrent infection, such as tonsillitis, or anything that has caused a reaction. These patients are also apparently benefited by ligation. We have noted that the patients who have the sharpest reactions after ligation often show the most improvement when they return in three months for thyroidectomy. Neuhof was unable to show uniform changes following experimental ligation of the thyroid arteries and veins in dogs.

The inferior thyroid artery plays such an important part in the mechanism of production and in the surgery of substernal and intrathoracic goiter, that it is worthy of consideration here. The inferior artery ascends in the neck behind the carotid sheath, emerging from between the layers of the prevertebral fascia only a short distance before it enters the capsule on the posterior surface of the gland. This affords a good anchorage for the lower portion of the lobe. Below this point there is considerable gland without any inferior attachment, save the inferior thyroid veins, and they give little or no support. An adenoma developing in this area will follow the line of least resistance, and hence grow downward between the middle and prevertebral layers of the deep cervical fascia, into the mediastinum. In removing such a gland it is important to begin at the superior pole and work downward, dividing the inferior thyroid artery close to the gland before attempting removal, and thus avoiding serious hemorrhage. The control of hemorrhage in surgery of the thyroid, especially exophthalmic goiter, is still of serious importance.

Velpeau, Kocher, DeQuervain, Jones, and others, routinely dislocate the gland inward, ligate the inferior thyroid arteries, and then the superior vessels before starting the thyroidectomy. The objections to this procedure are the possibility of injury to the recurrent laryngeal nerve, and occasional tetany.

Certain surgeons place hemostats around the lobe with a tight rubber band beneath them, and cut the gland across above the hemostats, suturing the cut surface. Helgenberg recommends suturing the sternothyroid muscle or pieces of the sternocleidomastoid muscle to the bleeding surface of the remnant of the thyroid gland.

The running, over-and-over sutures, lock sutures, continuous mattress sutures, and interrupted mattress sutures have all been used, the last named being the most satisfactory. Murphy has often said that great care should be taken to see that every vessel is found, clamped, and ligated in order to insure hemostasis. After operation the patient should be made to cough or strain. This will cause bleeding from any veins that have collapsed and have not been ligated. Finally, the wound should be packed with gauze if there is any doubt about the hemostasis.

Postoperative hemorrhage is no longer a common occurrence. If it does occur, it comes on from a few hours to seventy-two hours after operation and is generally from an inferior thyroid vein or from a branch of the inferior thyroid artery. Often no definite bleeding point can be found. Hemorrhage after the third day is extremely rare and is always due to infection.

CONCLUSIONS

1. The thyroid has a very rich arterial and venous blood supply.
2. There is an extensive anastomosis not only between vessels of the same lobe, but also with those of the opposite lobe.
3. In the event of ligation of all four thyroid vessels the circulation can be reëstablished through extraglandular anastomosis.
4. The secretory activity of the thyroid gland is under nerve control.
5. After ligation of the superior thyroid artery a polar ligation should be made in order to cut off the veins, lymphatics, and remaining nerve filaments.
6. Control of hemorrhage is best accomplished by interrupted mattress sutures placed through the remaining gland tissue, by ligation of all bleeding points, and by the use of gauze packing in the wound if necessary.
7. Bleeding veins can often be demonstrated by having the patient strain or cough before the wound is closed.

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STUDIES IN BASAL METABOLIC RATE*

ALBERT M. SNELL, FRANCES FORD, AND LEONARD G. ROWNTREE

Any method of determining the basal metabolic rate, to be of value, must yield under proper control, consistently normal values in normal persons and deviations from normal only when variations actually exist. In the studies reported, the gasometer method was employed, using the Tissot spirometer with the modifications introduced by Boothby and Sandiford, and Haldane's apparatus for analysis of the air. From an experience extending over fourteen months and involving approximately 750 determinations on 350 persons, the method was found to give results which vary only within normal limits.

As controls, a group was studied consisting of twenty-eight healthy students and nurses, the rate obtained falling within +10 and −10 per cent of the normals established by Du Bois. In twenty-five determinations on nine persons, the greatest variation found in the rates in an individual case was 10.5 per cent, the average variation being approximately 5 per cent. Reliable results can be obtained on out-patients after moderate exercise, provided they are subjected to from one-half to one hour of rest. The effect of a light breakfast, valued at approximately 200 calories, was determined on six subjects; the results agreeing with the findings of Soderstrom, Barr, and DuBois, that the metabolic rate returns to basal level in about three hours. Menstruation is perhaps a factor of some practical importance. In studies on a group of ten normal women students a rather constant rise occurred during menstruation or in the premenstrual period, the rise being followed by a postmenstrual fall.

Among the cases observed, hyperthroidism, polyglandular deficiencies, and afebrile conditions have yielded the lowest rates. Starvation and prolonged rest in bed tend to result in low rates.

In the study of the various diseases of the thyroid we have found

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Plummer's classification of great assistance. In a group of eight patients with cretinism and juvenile myxedema the metabolic rate varied from −7 to −25 per cent. No absolute parallelism between clinical manifestations and metabolic rate could be established, although some agreement existed. In a series of thirteen cases of exophthalmic goiter, the basal metabolic rate ranged from +20 to +82 per cent, rates being approximately proportional to the clinical evidence of thyroid intoxication. These patients and eleven patients with thyrotoxic adenomatous goiter were studied while under medical and surgical treatment. In one patient with recurrent exophthalmic goiter, a year subsequent to lobectomy, the rate did not respond to six weeks' rest in bed and courses of sodium cacodylate, but rapidly returned to normal, with marked clinical improvement, after roentgen-ray therapy.

Twenty-two patients with nontoxic adenomatous goiters had basal metabolic rates within normal limits. In twelve of fourteen girls presenting adolescent goiters, the rates fell within normal limits. In neither of the patients with high rates were there symptoms or signs of thyroid intoxication.

The basal metabolic rate of a group of seven patients with pituitary disease (Frohlich's syndrome and diabetes insipidus) has been studied together with the effect of pituitary extract in the treatment of such cases. From the data obtained it is evident that no profound or lasting effect on metabolic rate has resulted from the oral administration of the desiccated powder of the anterior lobe, or from the subcutaneous use of the extract of the posterior lobe and pars intermedia.

The fall of metabolic rate accompanying the period of fasting in the treatment of diabetes mellitus is striking, decreases of from 10 to 20 per cent being commonly encountered.

Several patients with leukemia and splenomegaly were found to exhibit a rate considerably above normal. The only instance of a subnormal rate in leukemia was in a case in which splenectomy had been performed some years earlier.

The effect of moderate doses of potassium iodid was investigated in seven subjects. In four patients with normal thyroids no increase in metabolism resulted, although in two of these the drug was administered to the point of iodism. Three subjects presented small adenomas and in each of these a marked increase in metabolic rate resulted. In a small series of patients with high rates, sodium cacodylate was administered subcutaneously in courses of 50 mg. daily for six days. The decrease in rate was not greater than could be attributed to the effect of rest in bed. On the basis of Hunt's work, in which he showed an increased tolerance for acetonitril in mice which were being fed thyroid, sodium cyanid in 3 mg. doses was administered two or three times daily to patients with exophthalmic goiter and toxic adenoma. In three cases an increased rate resulted, which is in accordance with Loevenhart's observations of the stimulating effect on respiration of small doses of cyanid. Whether continued administration would lead to a decreased rate was not determined, owing to some apprehension in regard to the use of the drug.

HISTOLOGIC STUDY OF THE EFFECT OF LIGATION OF THE THYROID VESSELS IN EXOPHTHALMIC GOITER*

ALFRED S. GIORDANO AND HAROLD D. CAYLOR

It has been observed for many years in the Mayo Clinic, that ligation of the thyroid vessels in patients with exophthalmic goiter is followed by distinct improvement of the clinical symptoms. Boothby's detailed study confirms the general opinion held at the Mayo Clinic.

The present study was made for the purpose of determining, if possible, whether any constant histologic changes could be demonstrated following ligation and, if such changes were found, whether or not they could be correlated with thyroidectomy, since no similar studies were found in the literature.

The thyroid glands studied were obtained immediately after thyroidectomy and sections taken from each pole at a point as near as possible to the entrance of the vessels into the gland. Other sections were taken from a point midway between the two poles, so that the gland tissue away from the ligated vessels served as a control with sections taken from fifty unligated hypertrophic parenchymatous thyroids.

The fifty cases of this series are divided according to the type of ligation into Group 1, fifteen cases of unipolar ligation; Group 2, twenty cases of bipolar ligation; Group 3, twelve cases of tripolar ligation, and Group 4, three cases of quadripolar ligation.

We have carefully studied the histologic picture of sections taken from the gland nearest the ligated vessels, noting particularly the size of the follicles, the type of epithelium lining them, and the amount of colloid present. The presence or absence of desquamation and pyknotic changes occurring in the nuclei, and the relative amount of intrafollicular fibrous connective tissue were noted. The changes found in the gland at the site of ligation were compared with those of the unligated portion.

The most constant finding of the early period in the sections taken near the ligated areas, was a tendency for the lumina of the follicles to be large and filled with colloid. The majority of these were lined with low columnar or cuboidal epithelium. The relic of the infolding of the wall of the follicles was represented by "sprig-like" processes projecting into the lumen (Fig. 135). Careful search revealed that the portion of the gland far from the entrance of the ligated vessels was surprisingly free from these changes and apparently more active than the one near the entrance of the ligated vessels, as shown by the abundance of parenchymatous hypertrophy. The epithelium lining the follicles in the ligated portion apparently tended to become cuboidal and, later, in areas, there was desquamation of the lining cells. Occasionally there were large, irregular, granular, deep staining, degenerative cells, described by MacCallum. In some of the late cases increase of the fibrous tissue stroma was the rule. This was most marked in the region of the capsule, near the thrombosed vessels, and extended into the neighboring parenchyma. In a few cases this change was so extensive as well to deserve the name given by Marine "cirrhosis of the thyroid gland." Pyknotic changes in the nuclei were also present in this type of degeneration.

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* Abstract of paper published in full in Surgery, Gynecology, and Obstetrics, 1923, xxxvi, 75–80. From the Section on Pathologic Anatomy, Mayo Clinic.

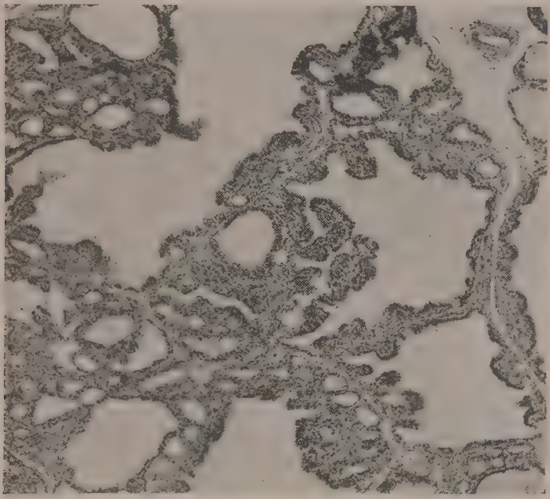

FIG. 135 (Case A346892).—Marked activity in the unligated pole; compare with Figure 136. (×50.)

The involution changes described, except thrombosis, have been invariably present in various degrees in hypertrophic parenchymatous thyroids whose vessels were not ligated, but in no instance were these changes circumscribed to and accentuated in any limited portion of the gland, as often noted after ligation. The following reports of cases illustrate the involution changes found in the ligated pole as compared with those in the unligated pole.

REPORT OF CASES

Case 1 (A346892). Mr. H. B., aged thirty-eight years, with exophthalmic goiter, had a basal metabolic rate of +94 per cent January 21, 1921. January 25 the left superior thyroid vessels were ligated and February 1 the right superior vessels were ligated. May 27 the basal metabolic rate had decreased to +62 per cent and during the interval of four months' rest the patient gained 15 pounds in weight, was stronger, and clinically much improved. June 1 partial thyroidectomy was performed. The portion of gland removed weighed 90 gm. The cut surface of the left upper pole of the gland near the entrance of the vessels was pale yellow to pink in comparison to the flesh color elsewhere. Microscopic sections revealed the follicles of the gland near the ligated vessels to be distended with colloid material. The epithelium lining these follicles was cuboidal. Scattered throughout the section were many sprig-like processes projecting into the lumen, and follicles lined by high columnar epithelium were present in only a few areas. Sections taken from the other poles were more active, as shown by the predominance of the typical architecture of hypertrophic parenchymatous thyroid (Figs. 135 and 136).

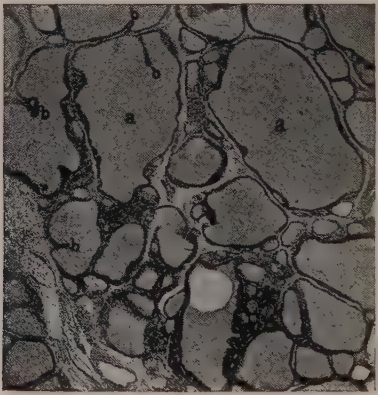

Fig. 136 (Case A346892).—Section taken from ligated pole 126 days after bipolar ligation: *a*, Predominance of large follicles lined with low cuboidal epithelium, and filled with colloid material. *b*, Sprig-like processes projecting into lumina of follicles. (×37.)

Case 2 (A346121). Mr. A. P., aged forty-four years, with exophthalmic goiter, had a basal metabolic rate of +77 per cent January 13, 1921, which gradually increased to +86 per cent February 7. February 15, and again seven days later, 5 c.c. of hot water was injected into the left lobe of the gland. The basal metabolic rate February 22 was +70 per cent. February 24 the left superior vessels were ligated. The patient returned to the Clinic the following July feeling better, although he had lost 14.5 pounds in weight during the interval. The basal metabolic rate was +84 per cent and the pulse rate 145. The patient was put to bed and roentgen-ray treatment was instituted. October 21 the basal metabolic rate was reduced to +58 per cent. The patient was sent home for further rest and returned the following December with a basal metabolic rate of +55 per cent and a gain of 26 pounds in weight. December 15 the right inferior and superior thyroid arteries were ligated and eleven days later both vessels on the opposite side were ligated. December 31 the basal metabolic rate was +39 per cent. The patient again went home and returned to the Clinic February, 1922, much improved. The basal metabolic rates were +36 and +41 per cent February 28 and March 1 respectively; a gain in weight was 29 pounds. March 2 bilateral partial thyroidectomy was performed. The portion of gland removed weighed 80 gm. Histologically, it showed marked diffuse parenchymatous hypertrophy (Fig. 137); definite histologic involution changes could not be found.

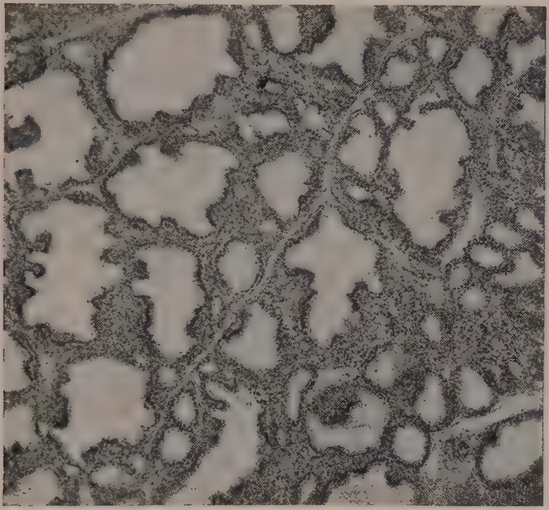

Fig. 137 (Case A346121).—Marked activity 221 days after quadripolar ligation. This is typical of the entire gland. (×50.)

Of the fifty cases of ligated hypertrophic parenchymatous thyroid studied in detail, definite involution changes were found in thirty-five (70 per cent), while sufficient distinguishing contrast between the ligated and unligated poles could not be demonstrated in the remaining fifteen. Definite involution changes were found in ten (66 per cent) of the fifteen cases of Group 1, in fourteen (70 per cent) of the twenty cases of Group 2, and in seven (46 per cent) of the fifteen cases of Groups 3 and 4 combined.

In the thirty-five patients with definite involution changes in the ligated pole, four showed slight or questionable changes, and fifteen showed no changes that could be attributed to ligation. No relationship between the time of ligation and that of partial thyroidectomy was demonstrable. A careful review of the clinical course of the disease following ligation disclosed that, on the whole, definite clinical improvement and a lowering of the basal metabolic rate occurred more often in cases in which definite involution changes were demonstrable in the ligated pole. On the other hand, eight definite and a few other probable but indefinite exceptions occurred; in these cases there was no evidence of correlation between the clinical symptoms and the histologic findings of involution changes. Our data do not indicate whether or not the involution changes noted following ligation of the vessels are attributable to the decrease in the blood supply or to the division of the sympathetic nerves accompanying these vessels.

In general, this study shows that distinct clinical improvement and lowering of the basal metabolic rate occurred more often in those cases in which definite involution changes in the ligated pole could be demonstrated histologically. On the other hand, a few definite exceptions demonstrated that a correlation between the clinical findings and the presence or absence of involution changes is not to be expected in all cases.

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DISEASES OF THE THYROID GLAND*

ARNOLD S. JACKSON

This thesis is an illustrated, detailed review under fifteen chapter headings, of the anatomy, embryology, histology, physiology, and biologic chemistry of the thyroid gland.

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* Thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, 1922. From the Section on Surgery, Mayo Clinic.

THE TOPOGRAPHIC ANATOMY OF THE THYMUS GLAND, WITH PARTICULAR REFERENCE TO ITS CHANGES AT BIRTH AND IN THE NEW-BORN*

GUSTAVE J. NOBACK

The material used in this study consisted of sixty-five fetuses and full-term infants. The specimens ranged from 10 to 55 cm. in length. Twenty-five of the infants were stillborn, and in twenty respiration had been at least partially established. Seven were observed at necropsy; the others had been preserved by intravenous injection of an aqueous solution of 10 per cent liquor formaldehyd and 1 per cent chromic acid. The material was studied by means of dissections, graphic reconstructions, and freehand sections.

The lobation of the thymus is determined early in fetal life and the establishment of respiration obviously has no effect on it.

The thymus in the late fetus and in the new-born is predominantly of the cervicothoracic type; that is, its position is intermediate between the cervical location in the embryo and the thoracic location in the older infant, child, or adolescent.

The thymus in the late fetus and stillborn child has a typical form and quite constant relations. Its lateral surfaces are convex and bulge against the medial surfaces of the lungs. The lungs very rarely extend on the anterior surface, and the thymus very rarely on the anterior surface of the right ventricle of the heart.

The thymus in liveborn infants has a typical form and relations similar to those found in young children. It is elongated and moulded so that its anterior, lateral, and posterior surfaces bear the impress of all the organs with which it is in contact. Its lateral surfaces usually show marked convexities occupied by the lungs, which pass over the anterior surface of this organ. Unlike the fetal thymus, it usually extends more inferiorly over the right ventricle.

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The change from the broad or fetal type of thymus to the elongated and moulded type found in the liveborn infant bears a direct relation to the establishment of respiration, and is dependent on the expansion of the lungs. The organ is compressed on both sides by the medial surfaces of the expanding lungs. It is compressed anteroposteriorly by the anterior borders of the lungs which early become much thickened in the establishment of respiration as they gradually overlap the thymus.

In some cases the thymic substance at birth may extend posteriorly to such an extent that the structures there are compressed by it. This may be due either to an unusually large thymus or to a very narrow, superior thoracic aperture which will not allow the thymus to protrude into the cervical region as it is compressed by the expanding lungs.

The descriptions and illustrations in the literature on the thymus in the new-born child show great confusion. They include both the fetal (broad) and infantile (narrow or elongate) types and the distinction between the two has evidently passed unrecognized. The type of thymus more often described as characteristic of the new-born and the infant is that which the data in this study indicate is usual for the fetus and stillborn as contrasted with the living infant.

T—'22—20

STUDIES IN DIABETES INSIPIDUS, WATER BALANCE, AND WATER INTOXICATION.

STUDY I*

JAMES F. WEIR, E. ERIC LARSON, AND LEONARD G. ROWNTREE

In a series of fifteen cases of diabetes insipidus no causative factor could be found in nine; four patients had syphilis, one had a supratentorial brain tumor, and one a pituitary tumor. The cardinal symptoms of the disease relate to disturbance of water metabolism. The fundamental question of priority of thirst or of polyuria was difficult to decide. In three cases there was a definite history of sudden onset with thirst; in two the thirst was primary, and in the third both thirst and polyuria came on suddenly. On the basis of Cannon's explanation of thirst as local in origin, cocainization of the nasopharynx and the administration of pilocarpin were tried, but without control of the thirst or polyuria. Thirst in this disease is more than an expression of dryness of the oral mucous membrane. Studies of renal function failed to incriminate any part of the urinary tract as an etiologic factor. Pituitary extract, administered with ureteral catheters in the renal pelves, controlled the polyuria in eight to ten minutes. This excludes constriction of the ureters as a controlling factor. Renal function was good in all cases; urine became concentrated under pituitary treatment.

In all cases of diabetes insipidus marked temporary results, lasting from a few hours to four to five days, followed the administration of extract of posterior lobe of the pituitary. No effects on the cardinal symptoms were obtained from (1) histamine, which differed entirely in its constitutional and local effects from those of posterior lobe extract; (2) spinal puncture with the removal of 5 to 10 c.c. of cerebrospinal fluid; (3) treatment for syphilis in the four patients with syphilis; and (4) restriction of fluids.

Metabolic studies were carried out in two cases and blood studies in four cases before and after the administration of pituitary extract subcutaneously. Balance of water intake and urinary output increased simultaneously with the decreased secretion of urine which was of higher specific gravity. This was accompanied by a gain in weight. After the effects of the drug wore off there was an increased excretion of water beyond the amount before treatment, and weight again dropped to normal. With the decreased water output under treatment there was slight decrease in the output of chlorin and nitrogen. In the blood the relative plasma volume was usually somewhat increased, and the molecular concentration, total nitrogen, and sodium chlorid were usually decreased. Thus, water retention was the most prominent feature during treatment. Blood volume determinations showed no constant demonstrable changes. Subcutaneous injection of 1 c.c. of pituitary extract produced no appreciable effect on the urinary secretion in average daily or three-hour periods, or on the specific gravity of the urine of five normal men under controlled conditions.

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Animals normally respond with a diuretic curve of urine secretion after the ingestion of large amounts of water. This can be abolished by pituitary extract, although continued administration of water overcomes the antidiuretic effect of 1 c.c. of the drug in a short time. If section of the renal nerves has been performed, similar results are obtained. During these experiments and in those on water intoxication no constant changes in total blood or plasma volume were demonstrable.

If patients with diabetes insipidus continue to ingest water in their accustomed amounts after the administration of pituitary extract certain signs of toxicity result; namely, headache, nausea, and vomiting. Similar effects are obtainable in animals, and, if continued, lead to the development of marked tremor, salivation, vomiting, diarrhea, frequent attempts at urination, asthenia, restlessness, drowsiness, ataxia on standing or walking, muscular twitchings, convulsions, coma, and death. Some of these symptoms are probably due to pituitary extract, although the majority are due to water. They usually develop after the ingestion of about 300 c.c. of water to each kilogram of body weight subsequent to the subcutaneous administration of 3 c.c. of posterior lobe extract. Similar results can be obtained after section of the renal nerves. The convulsions were characteristically epileptiform in type, a tonic phase followed by a clonic phase. Following the clonic phase the animals usually showed running, swimming, or snapping movements. With the development of these toxic symptoms there was a gradual marked rise of blood pressure. No definite pathologic changes were found at necropsy. A satisfactory explanation of these symptoms cannot be offered at the present time, although their similarity to the convulsions of uremia, eclampsia, and epilepsy are striking.

IV

BLOOD AND CIRCULATORY ORGANS

DESTRUCTION OF TRANSFUSED BLOOD IN NORMAL PERSONS AND IN PATIENTS WITH PERNICIOUS ANEMIA, AND ITS SIGNIFICANCE IN THE EXPLANATION OF THE ANEMIA OF PERNICIOUS ANEMIA AND OF NORMAL BLOOD DESTRUCTION*

WINIFRED M. ASHBY

My work was an attempt, by means of the study of the elimination of transfused blood, to throw light on the mechanism of normal red blood corpuscle destruction and on the anemia of pernicious anemia.

PART I

The study of the elimination of transfused blood has brought to light the fact that normally this elimination is not a continuous process, but takes place in more or less cyclic crises which seem to be more readily explainable on the basis of a destroying activity of the body than by the spontaneous degeneration of the blood corpuscle with their consequent removal. This apparent cyclic, destructive activity of the body toward transfused blood corpuscles is, in women at least, associated with a process which is under the influence of the endocrine gland system. If a parallel between the destruction of transfused and normal blood can be drawn, my investigation on transfused blood will make a contribution to our understanding of normal blood destruction in that it would seem to connect the process with an activity of the endocrine gland system.

METHOD

The elimination of transfused blood has been studied in patients whose bloods were in Groups I, II, and III, and who received Group

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* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota, in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1921. Published in full in the Journal of Experimental Medicine, 1921, xxxiv, 127–146; 147–166. From the Section on Experimental Bacteriology, Mayo Foundation.

IV transfusions. The method routinely followed consists of diluting the recipient's blood after transfusion with Group IV serum. This agglutinates the native corpuscles, leaving the transfused corpuscles free and capable of being counted in a hemocytometer. The dilution is made in a white blood-counting pipet, Group IV citrated serum being used as the diluent, and the mixture is expelled into Wassermann tubes. The tubes are incubated for forty minutes with shaking, and allowed to stand at room temperature for from fifteen to thirty minutes. A count is made by daylight, or, if it is necessary to use artificial light, care is taken to protect the corpuscles from its effects. All counts are made in duplicate.

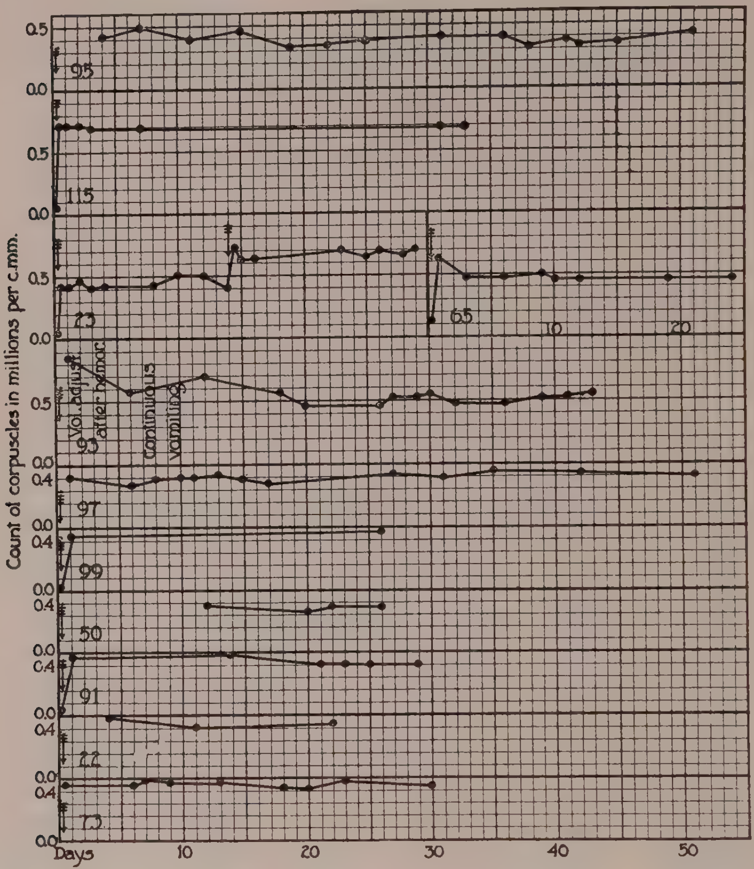

FIG. 138.—Curves showing that over a long period of time there is no elimination of transfused blood. ↧ indicates a Group IV transfusion.

With reference to the cyclic elimination of the transfused blood my material brings out five points:

1. The curves of elimination of Group IV transfused blood do not show a gradual downward trend day by day, which would be expected if it is assumed that blood corpuscles gradually wear out and are replaced. When due allowance has been made for changes in blood volume, it will be seen that the count stays on a level for a long time.

2. When counts have been taken sufficiently close together, the curve of elimination makes a sudden drop to a lower level, at which it again remains for many days. There are longer periods of no elimination and shorter periods of elimination.

3. The nature of these drops is such that they are more likely to be due to an active destruction on the part of the body than to, what would be the other possibility, a coincident spontaneous disintegration of the corpuscles.

4. Accompanying these drops in the count of the transfused blood there is usually an activity of the bone marrow as indicated by a rise in the total blood count.

5. In women these drops are related to the menstrual cycle.

The data, contributing to my first proposition that transfused blood corpuscles are not gradually eliminated day by day, but stay in the circulation without any appreciable decrease in their numbers for considerable lengths of time, are summarized in Figure 138.

PROTOCOLS OF CASES FROM WHICH THE DATA OF FIGURE 138 WERE DERIVED

Case 22.—A man, aged thirty-two years, weighing 103 pounds, had duodenal ulcer and chronic appendicitis. Posterior gastro-enterostomy and appendectomy were performed, followed by a transfusion.

Case 23.—A man, aged fifty-seven years, weighing 139.5 pounds, had pernicious anemia and was given a series of transfusions.

Case 50.—A man, aged fifty years, a farm laborer of powerful build, was given a transfusion after appendectomy and operation on the gallbladder.

Case 65.—A boy, aged eleven years, weighing 63 pounds, had lymphatic leukemia. He was transfused.

Case 73.—A woman, aged forty-seven years, weighing 120 pounds, had pernicious anemia, and was given a series of transfusions.

Case 91.—A woman, aged fifty-three years, weighing 137 pounds, had pernicious anemia, and was given a series of transfusions.

Case 93.—A woman, aged forty-three years, was given a transfusion because of postoperative hemorrhage after operation on the gallbladder. On the eighth and ninth days after transfusion subcutaneous injections of saline solution were given because of continuous vomiting.

Case 95.—A man, aged thirty-one years, had an arteriovenous aneurysm between the popliteal artery and vein, resulting from injury by a bullet. After operation secondary hemorrhage developed, necessitating a transfusion six days later. On the nineteenth day after transfusion the leg was amputated for dry gangrene. On the fifty-fifth day following hemorrhage a pelvic exploration was performed. The patient died on the fifty-seventh day after transfusion.

Case 97.—A man, aged forty-two years, weighing 155 pounds, had pernicious anemia and was given a series of transfusions.

Case 99.—A girl, aged seventeen years, weighing 100 pounds, was given a transfusion for secondary anemia due to malaria. Following medication there were no more chills.

Case 115.—A woman, aged thirty-three years, weighing 141 pounds, was given a blood transfusion January 26, 1920, because of secondary anemia. Normal menstruation occurred while the patient was under observation January 26, February 27, and March 24.

Data supporting propositions 2, 3, 4, and 5 are contributed by Figures 139, 140, 141.

PROTOCOLS OF CASES FROM WHICH THE DATA OF FIGURE 139 WERE DERIVED

Case 55.—A woman, aged fifty-one years, whose menopause had occurred two years before, was completely jaundiced from common duct obstruction. There was bile in the urine.

Case 116.—A man, aged twenty years, weighing 125 pounds, had been troubled with bleeding of the nose for the past nine years. He had a bleeding time of forty minutes and a coagulation time of five and one-half minutes; platelets were 88,000, and hemoglobin 43 per cent. The diagnosis was hemorrhagic purpura. One transfusion was given January 29, 1920. March 20 the hemoglobin was 80 per cent.

Case 119.—A man, aged thirty-three years, with a cystic tumor at the base of the tongue, came for examination because of sudden hemorrhage. The patient's blood condition rapidly returned to normal after transfusion and he was able to go to work.

PROTOCOLS OF CASES FROM WHICH THE DATA OF FIGURE 140 WERE DERIVED

Case 6.—A woman, aged thirty-five years, weighed 138 pounds. An operation for fibroma of the uterus was performed, followed by two transfusions because of severe hemorrhage.

Case 9.—A woman, aged thirty-three years, whose normal weight was 100 pounds, was transfused previous to subtotal hysterectomy. The convalescence was satisfactory.

Case 96.—A woman, aged forty years, had a malignant pelvic tumor. A total hysterectomy was performed, followed by a blood transfusion.

PROTOCOLS OF CASES FROM WHICH THE DATA IN FIGURE 141 WERE DERIVED

Case 38.—A woman, aged thirty-two years, weighing 133 pounds, in good general health, had multiple lipomas, which were removed. The following day a transfusion was given because of postoperative hemorrhage. Convalescence was excellent. Menstruation began the thirty-fifth day after transfusion and ended the thirty-eighth day.

Case 47.—A woman, aged forty years, weighed 105 pounds. A partial thyroidectomy was performed, which was followed by a transfusion. The patient made an uneventful recovery. Menstruation began the thirty-seventh day after transfusion.

Case 48.—A woman, aged forty-eight years, weighing 127 pounds, had cancer of the breast with extensive glandular involvement. The menstrual periods had been regular up to February 7, 1919. There was no further menstruation until March 28, when the menstrual flow began and continued until April 23. If the menstrual periods had continued to be regular after February, they should have occurred March 7, April 4, and May 2. April 5 a radical operation was performed, followed by a transfusion.

Case 68.—A woman, aged thirty-six years, weighing 82 pounds, had pernicious anemia. The patient claimed that her menstrual period was usually twenty-four days. While she was under observation menstruation occurred, beginning three days before transfusion, June 24, 1919. Menstruation did not occur July 18 when it was expected. The patient died August 24.

Case 92.—A woman, aged forty-nine years, weighing 215 pounds, had bleeding uterine fibromas, marked secondary anemia, and a degenerating colloid goiter. Three transfusions were given, two of which were of Group IV blood, after which partial thyroidectomy was performed. Menstruation began eleven days after the last Group IV transfusion, but stopped immediately, although previsouly bleeding had been profuse.

Case 103.—A woman, aged thirty-two years, had pernicious anemia and received a series of transfusions. While under observation profuse menstruation took place, beginning the twenty-fourth day after the Group IV transfusion.

Case 115 was also included in Figure 138.

RESULTS

In examining these curves it must be borne in mind that several factors other than blood elimination will bring about changes in the corpuscle count. Of these the most important is due to dilution from increase in blood volume, which may take place over a considerable period. It is probable, too, that changes in the capillary circulation cause changes in the count of the blood taken from the ear which do not represent changes in the average corpuscle content. There also seem to be daily changes in the blood volume in certain patients. Curves are very much smoother if the counts have all been made at the same time of day.

It will be seen that no definite elimination is shown in the curves there represented. Except for slight changes in the counts capable of the interpretations just suggested, as in Case 93, in which there was undoubtedly blood volume adjustment after hemorrhage and vomiting, these curves show no decrease in the count of the Group IV transfused blood corpuscles for fifty-one, fifty-one, forty-three, thirty-three, thirty, twenty-nine, twenty-six, twenty-six, twenty-four, and twenty-two days respectively. As these curves maintain a level for a long time, indicating that during that time there was no elimination, it is obvious that the blood is not eliminated by a continuous process, but by an intermittent process. In Figures 139, 140 and 141 it will be seen that there were sharp nonreversible drops in the count that must be attributed to elimination of corpuscles, following periods during which there was no decrease in the count of the tranfused blood corpuscles that could not be accounted for by changes in blood volume, and so forth. These periods of elimination compared with the periods of nonelimination are short and constitute crises of destruction.

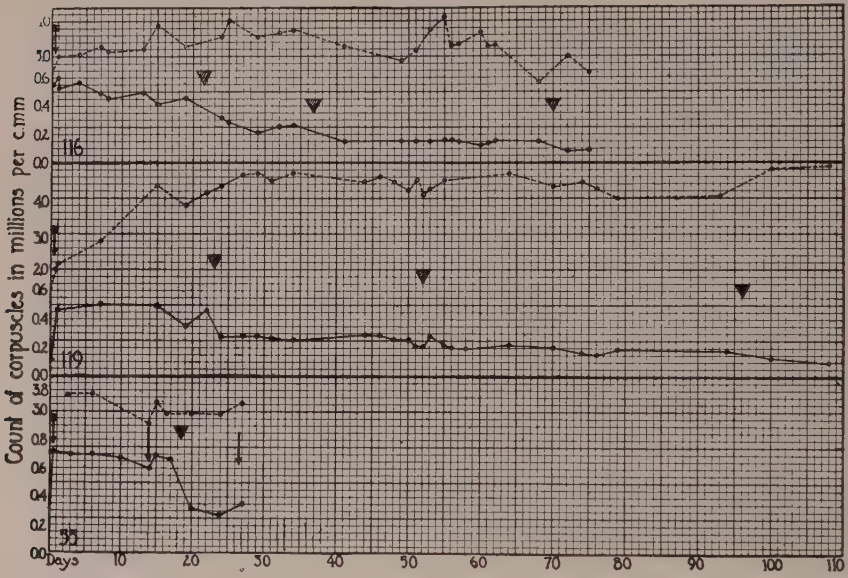

Fig. 139.—Curves of elimination of Group IV transfused blood in two men, and a woman past the menopause, showing that there are comparatively short periods of elimination and that these periods are irregularly cyclic. ——— Count of unagglutinated corpuscles. – – – Total red blood count. ↧ indicates a Group IV transfusion; ↑ a like group transfusion. The triangle calls attention to periods of elimination.

If the nature of the drops in the curves of Cases 116 and 119 in Figure 138 are examined, it will be seen that they are such as to suggest a blood-destroying activity on the part of the body rather than a spontaneous disintegration of simultaneously formed corpuscles. For if we postulate a blood destruction which is dependent solely on the condition of degeneracy of the corpuscle we shall have to assume not only that blood formation takes place in short periods, which may be the case, although the continued presence of reticulated corpuscles would seem to indicate that there is at least some continous formation, but also that the individual corpuscles are so uniform that the wear and tear which they experience after three months (Case 119) in the circulation

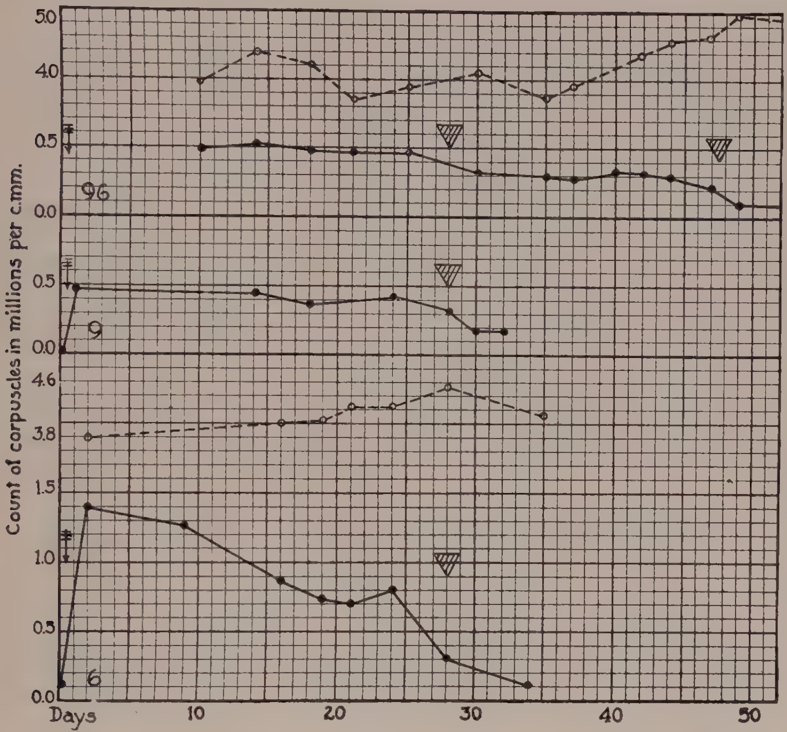

FIG. 140.—The drops in the curves of elimination of transfused blood of three women who received a transfusion at hysterectomy. The drops took place at approximately the same time after operation. ——— Unagglutinated corpuscles. – – – Total red blood count. ↧ indicates a Group IV transfusion. The cross-hatched triangle calls attention to periods of elimination.

bring them to a simultaneous disintegration point. But even if we are willing to make this assumption, further examination of the figures does not bear out this hypothesis. For if the condition of wear and tear were wholly responsible for initiating the destruction of the corpuscles we should expect a regularity in the rate of their disappearance. If, for instance, the corpuscles which were transfused had been formed in sharp crises every three weeks and their life were twelve weeks, then one-fourth of the corpuscles was due to live twelve weeks, one-fourth nine weeks, one-fourth six weeks, and so on. Equal amounts should

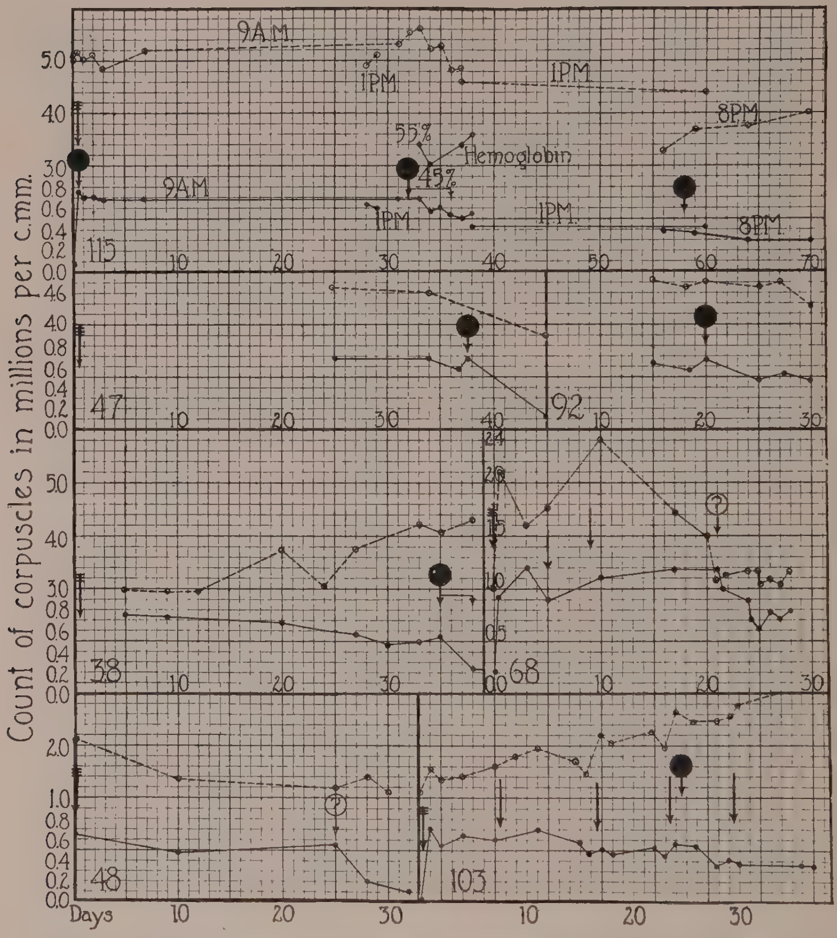

Fig. 141.—Curves illustrating the drop in transfused blood that takes place at the menstrual period. ↥ indicates the beginning of a menstrual period; ↧ indicates the time at which menstruation should have occurred. ——— Unagglutinated corpuscles. – – – Total red blood count. ⤓ indicates a Group IV transfusion; ↓ a like group transfusion.

have disappeared at each period of elimination. But this was not the case; by far the largest fall came in the first periods of elimination. In Case 119 the first drop was 200,000, or nearly one-half of the blood transfused, while subsequent drops were each approximately 80,000, or one-fifth of the original blood injected. In Case 116 the first drop was 150,000, or three-eighths of the blood injected, while subsequent drops were 90,000 and 80,000, about two-tenths of the injected corpuscles. These figures seem to place the elimination with reference to some active process on the part of the body, probably modified by the condition of the corpuscles and the number present in the circulation. Figures 139 and 140 contain data supporting the proposition that the crises of destruction of transfused blood, in women at least, show a relationship to a periodicity of function of an organ, the uterus, which is influenced by the endocrine gland system.

In Figure 140 are included the curves for the three women who received Group IV transfusions immediately before or subsequent to hysterectomy. In each case a period of elimination came between the twenty-fifth and thirtieth days after hysterectomy. The elimination would probably have proved to be sharper if the counts had been taken closer together. In one of these women a second period of elimination occurred about twenty days after the first. This suggests, although the series is too short to have a conclusion drawn from it, that in some way the hysterectomy initiated a cycle equivalent to the menstrual cycle, and when complete elimination did not take place the subsequent periodicity of elimination was irregular as in the case of the two men.

Figure 141 summarizes all the data that I have been able to obtain on the relationship between the elimination of transfused blood and the menstrual period. Six menstruations and two periods when menstruation should have occurred were observed. There has been no exception to the fact that elimination of transfused blood, not accounted for by simple blood loss from the menstrual flow, occurred during the menstrual period. It has not always happened that there was an elimination of transfused blood when menstruation should have occurred. In the two cases in which the elimination did occur without the appearance of the menstrual flow the women were in a condition of extreme anemia, and it is probable that the suppression of the flow was due to the anemia rather than to the suspension of the menstrual cycle.

In Case 115, which was the most intensive study made, the patient's blood volume was low and her count showed a great variation during the day, being much higher in the morning than in the evening, so that only counts taken at the same time of day were comparable. Those taken through the menstrual period that came thirty-two days after transfusion were made in the morning by one observer; those during the menstrual period that came fifty-eight days after transfusion were made by a second observer, and in the evening. The count which determines the farther end of the line connecting the two menstrual periods was made by the first observer at 1 p.m. The nearer end of the line is determined from a calculated figure. It will be noted that during the earlier menstrual period, although there was a decrease in the total red blood cell count, there was some increase in the hemoglobin. At this time the transfused blood had a higher index than the patient's blood, being 0.7 per cent, while the patient's blood was 0.5. During the later menstrual period there was a rise in the total blood count. In Case 38, with a very slight menstruation, there was an elimination of more than half the transfused blood; the preliminary fall in this curve is due to blood volume adjustment. There had been massive hemorrhage and the patient's blood volume was low. In Case 103, that of a patient with pernicious anemia, although the menstrual flow was profuse, there was a moderate fall in the transfused blood and a slight increase in the total count. In Case 48, in which menstruation did not occur when due, there was a complete elimination of the transfused blood with a slight temporary rise in the total blood count. In Case 68, one of pernicious anemia, a big fall in the Group IV transfused blood occurred beginning the twenty-first day, which may have been in part due to improvement in blood volume, since the patient's blood volume had been exceedingly low, and her general condition, in the face of what seemed to be a period of blood loss, became no worse. There was, however, at this time a marked elimination of the native corpuscles and of like group corpuscles, since the difference between the patient's whole blood count and the count of the transfused blood became so slight that it was within the limit of experimental error. From the twenty-first to the twenty-fifth days the difference between the two counts increased again, which, in view of the practically complete elimination of the patient's own blood, must indicate a coincident blood production.

DISCUSSION

There seems to be little doubt that the elimination of Group IV transfused blood is brought about by an active destroying process of the body which is some part of a metabolic cycle, evidenced in women by menstruation. Whether the Group IV transfused blood is eliminated as part of a general blood-eliminating effort of the body, or whether it is eliminated as a foreign body is a matter of interest. The fact that the

Group IV transfused blood stays in the circulation for considerable lengths of time is an argument against its foreign relationship to the body. On the other hand, in my studies of Group IV transfusions in patients with pernicious anemia, the Group IV transfused blood has remained in the circulation in the presence of destruction of the patient's own blood, and in one instance, Case 68, in the presence of destruction of transfused blood of the same group as the patient's. It would seem that if the elimination of the Group IV blood takes place because of a normal blood-eliminating process, either there must be two processes, one of which can handle the blood of the unlike group, while the other cannot, or else that a certain pressure of elimination must be attained before the threshold is reached for the elimination of Group IV corpuscles which are apparently more difficult to destroy. Unless it is assumed that some Group IV transfusions are, relative to the patient's own blood, less enduring than others, the latter would not seem to be the case because in some instances we have seen complete elimination of the transfused blood in one elimination period, which would, on the assumption of a higher threshold mechanism, necessitate tremendous coincident elimination of the recipient's blood. If we assume two processes at work in the physiologic elimination of blood, one of which is more able to handle the apparently slightly foreign Group IV blood, we might conceive of it as part of a more general lytic or phagocytic function which has as one of its expressions of activity the sloughing of the endometrium and which is able to overstep the group differences. On the other hand, this periodic elimination of transfused blood may not be due to any specific blood-eliminative activity, but to a nonspecific eliminative activity.

It would be a matter of great interest to know whether or not normal physiologic blood elimination also takes place in sharp cyclic crises. Satisfactory evidence on this point is difficult to obtain because if there is such blood elimination it may be masked by production, or if there is any apparent drop in the total blood count we do not at present know that it is not due to changes in blood volume or to an uneven distribution of corpuscles.

SUMMARY AND CONCLUSIONS OF PART I

Group IV transfused blood in a recipient of unlike group is eliminated by a blood-destroying activity of the body.

This blood-destroying activity is periodic both in men and women, and in women coincident with menstruation.

The elimination of the transfused blood probably takes place as part of a period of blood-destroying and blood-producing activity of the body, although direct evidence to this effect is so far lacking.

PART II

An attempt was made to obtain an understanding of the mechanism by which blood destruction is brought about through the study of the elimination of Group IV transfused blood. The object of the study was to answer the question as to whether there is any hemolytic toxin at work in pernicious anemia by comparison of the curves of elimination of Group IV transfused blood in cases of pernicious anemia with those obtained from patients without blood disease. As a control, patients with other diseases, in which it was suspected that there might be increased blood destruction, were chosen for transfusion. It was hoped that if no excessive destruction of Group IV blood resulted, data might be obtained that would give some clue as to which of the other two possibilities, namely, the intrinsic weakness of the corpuscle or the speeding up of normal blood destruction, is responsible for the anemia.

Many of the older writers inclined to the idea that pernicious anemia is fundamentally a failure in erythrogenesis, but in the light of recent investigation it is more generally assumed that increased blood destruction is the important cause of the anemia seen in this disease. This assumption rests mainly on increase in hemosiderin deposits in the tissues, and in the output of bile pigment, the rapid falls that are seen in the blood count, and the anemia in the face of what is apparently a hyperplasia of the bone marrow. My own results of the study of thirty-three cases of pernicious anemia in which Group IV transfusions were given have not shown the intensive blood destruction I expected.

On going over the literature of the subject I find it possible to put more than one interpretation on these facts of increased hemosiderin deposits, bile excretion, and so forth, which are usually assumed to be evidence of a high rate of blood destruction in pernicious anemia. The increased activity of the bone marrow as judged by the increased density of mitotic figures and immature cells and the increased mass of erythropoietic tissue may be only apparent. If there were some factor present which retarded the speed of the process of maturation and division, while the physiologic stimulus to erythrocyte production brought into play by the anemia caused an increase in the number of cells dividing, we might have such a picture with a decrease in the total cell output. The hemosiderin deposit is evidence only that iron is not being kept in circulation. This may be due to abnormal destruction of hemoglobin, but it is equally possible that it is due to a failure to utilize iron, released by a normal rate of blood destruction, sufficiently quickly in the formation of new hemoglobin. Increased output of bile pigment cannot be accepted as evidence of increased blood destruction because Whipple and Hooper have shown that bile pigment is derived from other sources besides hemoglobin. It is conceivable that with a depression in protein synthesis the pigment material which might have combined with globin to form hemoglobin is diverted to the increase of the bile pigment output. Urobilin and urobilinogen in the duodenal content and urine, although they may appear in these excretions when there is blood destruction, are only evidence that bilirubin has been reduced before it reaches the intestinal tract, or that it was incompletely synthesized. Rapid falls in the blood count can be explained just as plausibly on the basis of a failure of production and the physiologic end of the corpuscle as its abnormal destruction. All these facts of hyperplastic bone marrow, increased bile pigment, and so forth, which from one angle seem to point collectively toward excessive blood destruction, by changing the point of view can be made to present just as solid a front against it. I do not feel that our laboratory studies of pernicious anemia offer anything that can be accepted as absolute proof of excessive blood destruction.

Perhaps we have our best evidence of blood destruction in pernicious anemia when on transfusion the total count fails to increase or even decreases, and when the symptoms of the patient do not indicate any blood volume improvement. Since I have already shown that there is no intrinsic destructibility of transfused blood, even of citrated transfused blood, this failure of the corpuscle content to increase when corpuscles are injected is evidence of corpuscle destruction. This situation, however, is the occasional one and, unless the patient succumbs, is only temporary. It is evidence that there are at least intermittent periods of destruction, but it does not support the idea of certain investigators of a continuous destruction.

RESULTS

The technic used was that already described. Thirty-three patients with pernicious anemia not of Group IV were given Group IV transfusions. Four of them were under observation for about three months, ten were observed for one month or more, eight for at least seventeen days, and the rest for shorter periods of time.

PROTOCOLS OF CASES FROM WHICH THE DATA FOR FIGURE 142 WERE DERIVED

Case 43.—The patient was a man, aged forty-nine years, weighing 163 pounds. He had no free hydrochloric acid in the stomach. He had glossitis and combined sclerosis of the cord. The red cell count was 1,900,000, the hemoglobin 44 per cent, and the color index 1.4+. The white count was 3,400 and the lymphocytes 36 per cent. There was marked anisocytosis and moderate poikilocytosis. Diagnosis of pernicious anemia was made. A series of six transfusions of 500 c.c. of citrated blood was given.

Case 57.—The patient was a man, aged sixty-three years, weighing 157 pounds. He complained of a general increase in weakness, beginning two years before, when he became sallow and lost his appetite, and his legs swelled. There were glossitis and numbness and tingling in the feet. The red blood count was 1,136,000, hemoglobin 25 per cent, color index 1.1+, leukocytes 4,200, polymorphonuclear neutrophils 44 per cen, lymphocytes 56.5 per cent, normoblasts 3 per cent, and marked anisocytosis and poikilocytosis. Diagnosis of pernicious anemia was made. A series of eight transfusions of 500 c.c. of citrated blood was given.

Case 59.—The patient was a short woman, aged fifty-two years, weighing 149 pounds. In February, 1918, when she first came for examination, she was sallow and weak, and had numbness of hands and feet, and a smooth tongue. Her red blood count was 1,900,000, color index 1.1+, leukocytes 3,400, and lymphocytes 72 per cent. There were moderate anisocytosis and poikilocytosis. Diagnosis of pernicious anemia was made. She was given 2,500 c.c. of blood in three transfusions in the course of a month; this was followed two months later by two transfusions of 500 c.c. In May, 1919, she returned, with a red blood count of 1,330,000 and was given one Group IV transfusion of 500 c.c., after which she improved and maintained a fairly good count.

Case 97.—The patient was a man, aged forty-two years, weighing 155 pounds. His chief complaint was weakness. He had been gradually losing strength for three years. He had glossitis, absence of free hydrochloric acid in the stomach, and tingling and numbness of the arms and legs. His red blood count was 2,240,000, hemoglobin 50 per cent, color index 1.1—, and leukocyte count 4,000. The diagnosis was pernicious anemia. The patient received a series of five transfusions of 500 c.c. of citrated blood. Later he returned for other transfusions.

Of the four pernicious anemia patients (Fig. 142) who were studied until the elimination of transfused blood was complete or almost complete, the time taken for complete elimination in two instances was ninety-one days (Case 43) and 100 days (Case 59) respectively. In another (Case 97) elimination was not complete in 100 days, and in the fourth (Case 57) there were still some transfused corpuscles after eighty-three days. These curves compare well with the longest complete curve of elimination obtained in a normal individual and are much longer than the other seven completed curves obtained for individuals without blood diseases. Of these four patients, in one instance (Case 59) the transfusion brought about a remission which lasted for over a year.

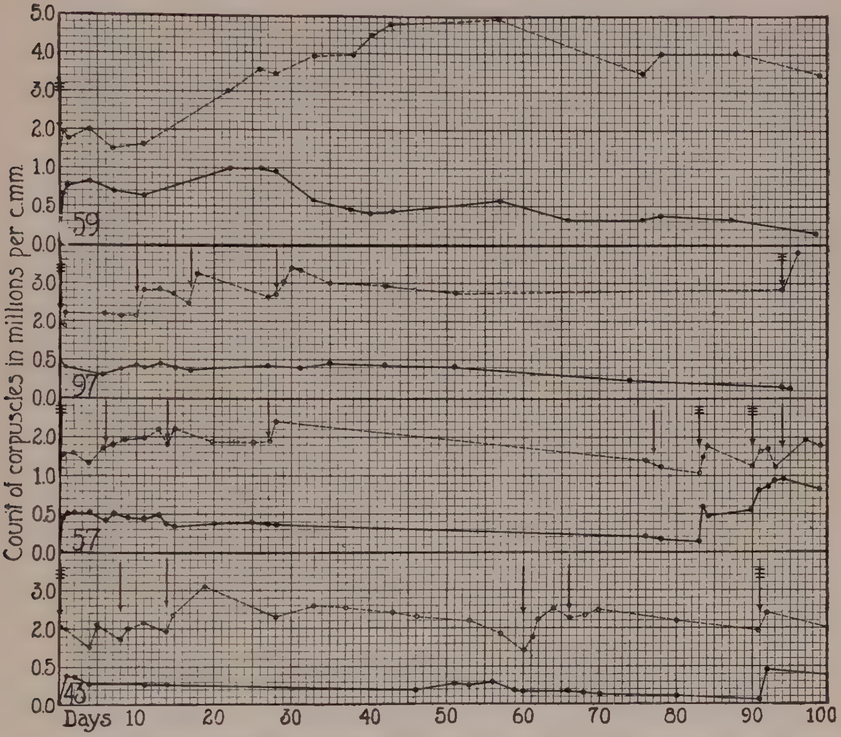

FIG. 142.—The curves of elimination of 500 c.c. of Group IV transfused blood of four patients with pernicious anemia, studied until elimination was complete or nearly complete. ——— Unagglutinated corpuscles. – – – Total red blood count. ‡ indicates a Group IV transfusion. ↓ a like group transfusion.

In the other three cases it was necessary to give repeated transfusions during the time that the patients were under observation.

PROTOCOLS OF CASES FROM WHICH THE DATA FOR FIGURE 143 WERE DERIVED

Case 23.—The patient was a man, aged fifty-seven years, weighing 139.5 pounds. He had suffered from weakness for seven years. Two years before he had had a blood count of 3,500,000, a color index of 0.9+, glossitis, and posterior sclerosis, and a diagnosis of pernicious anemia of the neurotic type had been made. One year later the patient returned, with a red blood count of 1,090,000, hemoglobin 26 per cent, color index 1+, leukocytes 3,800, and red cell count 830,000. A series of four transfusions of 500 c.c. of citrated blood was given.

Case 26.—The patient was a man, aged forty-four years, weighing 148.5 pounds.

The skin was lemon yellow, the tongue atrophic, and there was a systolic murmur over the base of the heart. He complained of weakness, which began seven years before. The hemoglobin was 32 per cent, red blood count 1,480,000, color index 1.1+, and leukocyte count 2,600. A diagnosis of pernicious anemia was made. The patient received a series of transfusions in 1918. He received transfusions in January, 1919, and again in May, 1919.

Case 60.—The patient was a man, aged thirty-six years, weighing 137 pounds. He was pale and extremely weak. The neurologic examination showed combined sclerosis. There was no glossitis. A test meal was not given. The blood picture was typical of pernicious anemia. A diagnosis of pernicious anemia was made. Three transfusions were given, with improvement in the patient's condition. There have been subsequent remissions.

Case 61.—The patient was a man, aged forty-two years, weighing 152 pounds. There were weakness and combined sclerosis. The red cell count was 1,510,000, hemoglobin 34 per cent, color index 1.1+, leukocyte count 2,000. A diagnosis of pernicious anemia was made. Four transfusions of 500 c.c. of citrated blood were given.

Case 73.—The patient was a woman, aged forty-seven years, weighing 110 pounds. Her chief complaint was weakness. July 28, 1919, the red count was 1,750,000, hemoglobin 34 per cent, color index 0.9—, and leukocytes 5,000. There was marked anisocytosis. No test meal was given, but digestion improved with hydrochloric acid. Neurologic examination showed spinal sclerosis of the pernicious anemia type. A diagnosis of pernicious anemia was made. The patient received a series of transfusions and returned home, where more transfusions were given. She died May, 1920.

Case 79.—The patient was a man, aged twenty-five years, weighing 126 pounds. He had a palpable spleen, and there was no free hydrochloric acid in the stomach. The neurologic examination was negative, and there was no evidence of glossitis. The red cell count was 1,120,000, hemoglobin 23 per cent, color index 1, leukocyte count 4,800, neutrophilic myelocytes 4.5 per cent, normoblasts 4 in a count of 200, and megaloblasts 1. A diagnosis of pernicious anemia was made. Three transfusions of 500 c.c. of citrated blood were given. Since then the patient has returned twice for transfusions.

Case 80.—The patient was a man, aged thirty-four years, weighing 154 pounds. He had a bald tongue, but no evidence of combined sclerosis. His chief complaint was weakness and indigestion. The red cell count was 1,960,000, hemoglobin 40 per cent, color index 1+, leukocyte count 6,400, and small lymphocytes 48 per cent. There were moderate anisocytosis and poikilocytosis. Diagnosis of pernicious anemia was made. On the fifteenth day after transfusion the patient took magnesium sulfate, preparatory to stool examination. Two transfusions of 500 c.c. of citrated blood were given.

Case 89.—The patient was a woman, aged sixty years, who normally weighed 180 pounds and at the time of examination 127 pounds. Her chief complaint was weakness. Transfusions elsewhere had improved her condition. She had pigmented skin, sore tongue, and no free acid in the stomach. The red blood count was 1,820,000, hemoglobin 38 per cent, and color index 1. The leukocytes were 6,200, lymphocytes 33.5 per cent, and normoblasts 1 per cent. There were marked anisocytosis and poikilocytosis. Diagnosis of pernicious anemia was made. A series of four transfusions of 500 c.c. citrated blood was given.

Case 91.—The patient was a woman, aged fifty-three years, weighing 137 pounds. She showed marked weakness, glossitis, dyspnea, short pulmonic systolic murmur, edema, and early symptoms of combined sclerosis. Her color was lemon yellow. Red blood cell count was 1,440,000, hemoglobin 35 per cent, color index 1.24, and leukocytes 6,600, with polymorphonuclear neutrophils 56 per cent, small lymphocytes 39.5 per cent, large lymphocytes 2.5 per cent, eosinophils 1.5 per cent, neutrophilic myelocytes 0.5 per cent, normoblasts 1.5 per cent, megaloblasts 0.5 per cent, and moderate anisocytosis and poikilocytosis. The diagnosis was pernicious anemia. Three transfusions of 500 c.c. of citrated blood were given.

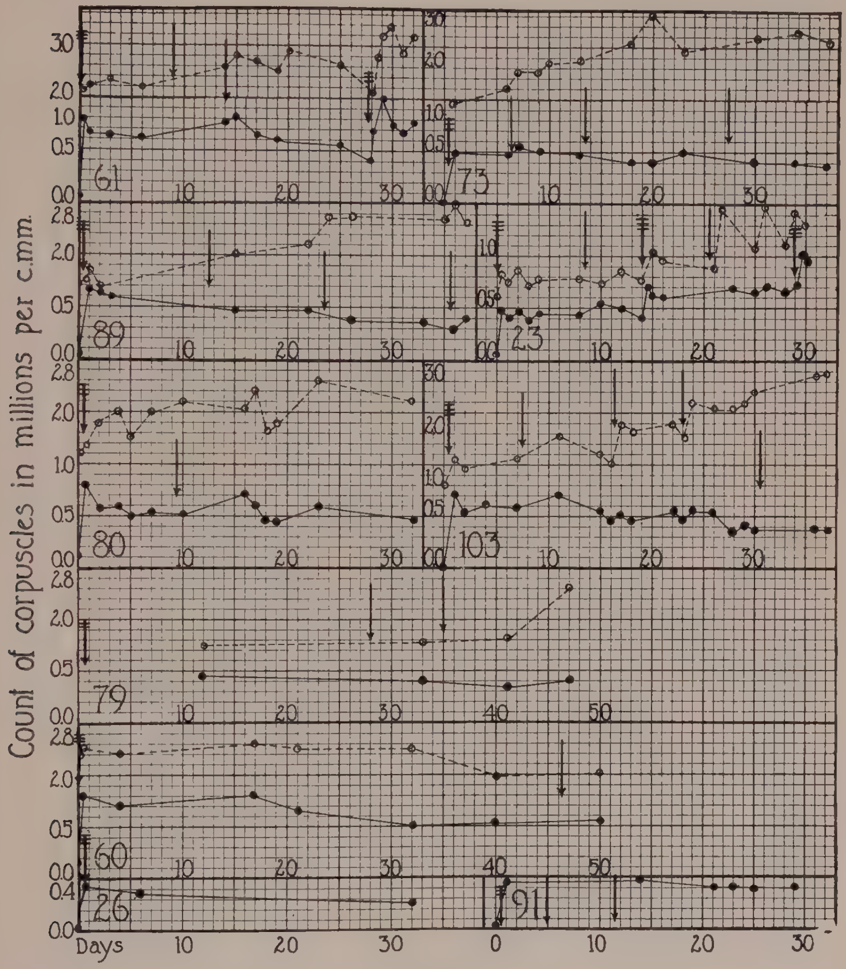

FIG. 143.—Elimination curves of Group IV transfused blood in ten patients with pernicious anemia under observation for thirty days or more. ——— Unagglutinated corpuscles. – – – Total red blood count. ↡ indicates a Group IV transfusion; ↓ a like group transfusion.

Case 103.—The patient was a woman, aged fifty-two years. She complained of weakness. She was well until a year before, when she had influenza. There were glossitis, posterolateral sclerosis, soft systolic murmur at the apex of the heart transmitted to the axilla, and retinitis of pernicious anemia. The spleen was palpable one inch. The red cell count was 960,000, hemoglobin 23 per cent, color index 1.2+, leukocytes 2,400, polymorphonuclear neutrophils 13.5 per cent, small lymphocytes 78 per cent, large lymphocytes 8 per cent, neutrophilic myelocytes 0.5 per cent, normoblasts 12 per cent, megaloblasts 1 per cent, and marked anisocytosis and poikilocytosis. While under observation profuse menstruation took place, beginning December 20, 1919. A series of four transfusions of 500 c.c. of citrated blood was given.

In the curves in Figure 143 it will be seen that in no case is there any elimination of Group IV transfused blood that cannot be duplicated in the control cases, and the majority do not show any drop as great as that which occurred in more normal individuals. In Case 89 the decline before the twenty-second day would seem to be blood volume improvement, as the patient's blood volume, calculated from the transfusion data immediately after transfusion, was low, being 6.4 per cent of the body weight, whereas the blood volume in secondary anemia as found by this method is from 8 to 9 per cent of the body weight. The same may be said of the apparent fall in Case 60. In Case 26 the count of unagglutinated corpuscles with a blood volume of 8.5 per cent would have been 342,000, so the count of this patient on the sixth day after transfusion

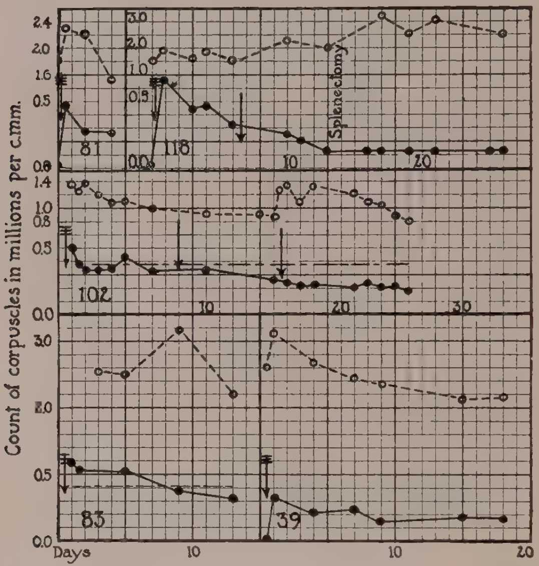

FIG. 144.—Control cases in which there appears to have been some progressive elimination of Group IV transfused blood. ——— Unagglutinated corpuscles. – – – Total red blood count. - - - - - The count of unagglutinable corpuscles that would be expected in an individual the size of a patient with a blood volume of 8.8 per cent of the body weight. ↧ indicates a Group IV transfusion; ↓ a like group transfusion.

was still more than the number that would have been present if a normal blood volume adjustment had been attained. As a count was not taken between the sixth and thirty-second days, while the patient was at home, data does not show when the drop, which occurred in the curve between those dates, took place. We have no reason, however, to assume that it was any sooner than would have been normal.

In contrast to the stability of transfused blood in cases of pernicious anemia is the elimination which was found to take place in certain patients with other pathologic conditions. In the cases which came under observation during the course of this study five appear to have shown a progressive and rapid elimination of Group IV transfused blood. This feature was most markedly shown in Case 118, one of hemolytic jaundice, in which there was a continuous fall in the curve of transfused blood until splenectomy, when the fall ceased sharply. Two cases of aplastic anemia (Cases 81 and 102, Fig. 144), one case of myelogenous leukemia (Case 39), and one of carcinoma of the kidney with metastasis show increased elimination of transfused blood.

PROTOCOLS OF CASES FROM WHICH THE DATA FOR FIGURE 144 WERE DERIVED

Case 39.—The patient was a man, aged fifty-five years, weighing 166 pounds. He had myelogenous leukemia with a white blood count of 215,000. A transfusion was given, followed after six days by radium treatment. Profuse sweating occurred the fifteenth day after transfusion, with edema of the eyes and forehead; on the eighteenth day the edema was extreme. The patient died on the nineteenth day.

Case 81.—A man, aged forty-five years, weighed 154 pounds. Diagnosis of aplastic anemia was made. The patient died of bilateral bronchopneumonia (August 29, 1919) on the fourth day after transfusion. There were miliary tubercles in the spleen.

Case 83.—The patient was a man, aged sixty-nine years, weighing 105 pounds. There was carcinoma of the left kidney, with metastasis. A left nephrectomy was followed by a transfusion with 500 c.c. of Group IV citrated blood.

Case 102.—The patient was a man, aged twenty-eight years, weighing 124 pounds. In October, 1918, he had influenza, which was followed by weakness and bleeding. There was severe epistaxis in October, 1919. At examination in November the red blood count was 1,160,000, the hemoglobin 13 per cent, and the color index 0.5+. The leukocytes were 10,800, with polymorphonuclear neutrophils 25 per cent, small lymphocytes 37.5 per cent, large lymphocytes 35.5 per cent, eosinophils 0.5 per cent, basophils 0.5 per cent, and neutrophilic myelocytes 1 per cent. There was moderate anisocytosis, and the platelet count was 134,000. December 9 the platelet count was 96,000. A diagnosis of aplastic anemia was made. Four transfusions were given. December 12 an eruption appeared on the arms and face, which proved to be smallpox. January 1, 1920, the patient died.

Case 116.—The patient was a boy, aged thirteen years, weighing 76.5 pounds. He was jaundiced and weak. He had an enlarged spleen, which had been first noticed three months before. The red blood count was 1,750,000 and hemoglobin 30 per cent, giving a color index of 0.8+. The white cell count was 19,500, with 65 per cent polymorphonuclears and 25 per cent lymphocytes. The platelets were 148,000 and the bleeding time one-half minute. There was increased fragility. The blood picture did not improve after two transfusions. There was no evidence of familial jaundice. A diagnosis of hemolytic jaundice was made. Splenectomy was performed and the patient regained normal health.

If the curves of the total red blood counts of the pernicious anemia patients are examined, it will be seen that there are some instances in which blood destruction is definite, although in most cases it would be difficult to say that there has been blood destruction during the preceding transfusion studies. In estimating these curves it must be borne in mind that changes in the blood volume very materially influence the total count. Changes in the number of transfused blood corpuscles for each cubic millimeter give some indication of changes in blood volume. When the transfused blood count rises it is probable that the blood volume decreases, and when the transfused blood count falls with a subsequent return, showing that the fall was not due to elimination, it is probable that the blood volume increases. This has been assumed in the following calculations:

In Case 23 on the tenth day after the initial Group IV transfusion the total count was 1,100,000; the Group IV transfused blood was 520,000 minus the initial unagglutination of 70,000, or 450,000. Since the subsequent Group II transfusion two days before was 100 c.c. larger than the Group IV transfusion, it should account for at least the same number of corpuscles. The total count before this transfusion had been 1,170,000 with apparently a larger blood volume, as the count of the unagglutinable corpuscles was less. There have been added at least 450,000 corpuscles for each cubic millimeter, the blood volume has decreased, which should have still further increased the total red cell count, but the total count is still what it was before transfusion. We have here evidence of destruction. In Case 61, on the fifteenth day after the Group IV transfusion, the total count was 2,250,000. The Group IV corpuscles were 700,000, so the two like group transfusions which had been given on the ninth and fourteenth days should have added 1,400,000, or twice that amount. The total count three days before these transfusions was 1,570,000, when the blood volume, judging from the unagglutinable corpuscle count, was somewhat higher; 1,400,000 corpuscles for each cubic millimeter have been added to the blood, the blood volume has decreased, which would still further increase the count, and the total count has increased only 680,000. Here there is a loss of over 700,000 corpuscles for each cubic millimeter in eight days. In Case 73, on the twentieth day after the Group IV transfusion, the total count was 3,000,000, and on the twenty-third day it was 2,300,000, with a decrease in blood volume, giving a loss of more than 700,000 corpuscles for each cubic millimeter. In Case 80, between the tenth and sixteenth days after the Group IV transfusion, during which time a like group transfusion was given, there was a decrease of 150,000, with a decrease in blood volume, following purgatives, of nearly one-third. Here the loss was over 800,000 cells for each cubic millimeter. In Case 29, at the time of the like transfusion given February 10, the total count was lower afterward than before, although the unagglutinated counts showed the volume to be about the same. In a case studied for twenty-six days there was a fall of 600,000 in the blood count in three days with no increase in volume to account for it.

Of course, it must be admitted that in these estimates we are omitting the consideration of one factor; we do not know what is happening on the blood production side. The destruction may be greater than it appears to be. The periods of destruction, however, are limited to certain parts of the curve. The blood destruction is by no means of the same order as that seen in the case of hemolytic jaundice studied. It is quite possible that it is of no greater magnitude than that which is probably connected with the cyclic elimination of transfused blood which has been seen to take place in normal individuals.

There are, however, two cases in which blood destruction seems to have been excessive. These cases are of especial interest because the blood destruction of the corpuscles of the like group was so great that practically nothing was left but Group IV transfused blood; Group II transfused corpuscles were eliminated with the patient's corpuscles.

In Case 57 (Fig. 142), on August 21, the count of unagglutinable corpuscles after two Group IV transfusions, which had been made subsequent to a Group II transfusion, was 940,000. The initial unagglutinated count was 10,000, making the Group IV corpuscles 930,000. The total count was 1,230,000, making a difference of 300,000 to account for the patient's own blood and a Group II transfusion given sixteen days before, which would at the time probably have given a count of 450,000. On the following day the count of unagglutinable corpuscles was still 940,000, while the total blood count was 930,000, or, within experimental error, the same. Unfortunately, however, this count was not checked by a duplicate tube as one of the tubes leaked in transit and a transfusion was given before we could get another count.

In Case 68 (Fig. 145) the patient, who had previously had a splenectomy, received a Group IV transfusion on June 27. The blood volume at the time was low, as the transfusion of 500 c.c. gave a count of 930,000 unagglutinated corpuscles. On the fifth and ninth days after the Group IV transfusion she received transfusions of 500 c.c. of Group II citrated blood. The day after the second like group transfusion the count of unagglutinated corpuscles was 1,120,000. Since the initial count of unagglutinable corpuscles was 230,000 (this is unusually high) we take 890,000 as the count of Group IV corpuscles.

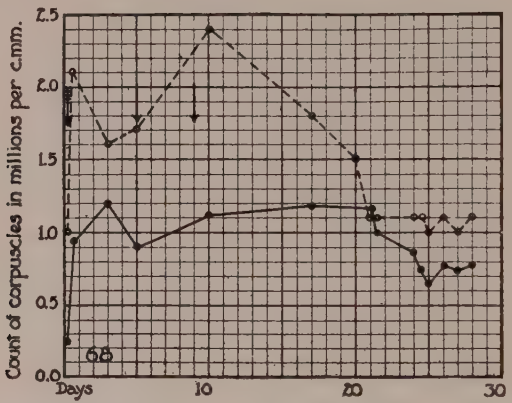

Fig. 145.—Curves of a patient who showed elimination of the Group II transfused corpuscles as well as elimination of her own. ——— Unagglutinated corpuscles. – – – Total red blood count. ↧ indicates a Group IV transfusion. ↓ a like group transfusion.

The two Group II transfusions with the same blood volume should have given 1,780,000 corpuscles for each cubic millimeter. The total count minus the Group IV count was 1,610,000. On the seventeenth day after the Group IV transfusion, the Group IV transfused corpuscles were 950,000 for each cubic millimeter; the Group II transfused corpuscles should have been at least 1,900,000 for each cubic millimeter, or twice the number of Group IV corpuscles. The total number of Group II corpuscles, including both the patient's own corpuscles and the transfused, was 850,000. On the twenty-first day the total blood count and the count of the unagglutinable corpuscles were equal within experimental error. There were practically no clumps in the field, and a large number of nucleated red cells in the film. The potency of the serum was checked. A count repeated in the afternoon gave 990,000 for the unagglutinable corpuscles, 760,000 for the Group IV corpuscles, and 1,100,000 for the total count. This would have left 340,000 Group II corpuscles for each cubic millimeter. Since the count of the transfused Group II corpuscles alone should have equaled 1,500,000, we have here undoubtedly an elimination of the Group II transfused corpuscles as well as elimination of the patient's corpuscles.

PROTOCOLS OF CASES FROM WHICH THE DATA FOR FIGURE 145 WERE DERIVED

Case 68.—The patient was a woman, aged thirty-six years, weighing 82 pounds. She was very weak. Elsewhere a diagnosis of pernicious anemia had been made, and splenectomy performed April 28, 1917, after which there had been very great improvement in the patient's condition. On June 24, 1919, the red blood cell count was 1,060,000, hemoglobin 28 per cent, color index 1.3, leukocyte count 7,400, and lymphocytes were 74.5 per cent. In the count of 200 white cells, eighty-nine normoblasts and three megaloblasts were seen. There were marked anisocytosis and poikilocytosis. Menstruation was expected on the twenty-first day after the transfusion, but did not occur. The patient died a month later.

Two cases early in the series, if they are valid, are exceptions to the rule that in patients with pernicious anemia there is no increased elimination of transfused blood. In these two cases complete elimination suddenly took place soon after transfusion. It is possible, however, that these apparent exceptions were due to faulty technic.

DISCUSSION

This study of patients with pernicious anemia during a series of transfusions seems to indicate that, although in some cases at certain times there is much blood elimination, on the whole, blood destruction is quiescent. Of course, it must be recognized that in this estimate the factor of production is an unknown quantity. Group IV transfused corpuscles are, as a rule, not eliminated so quickly as they are in transfused persons without blood disease, so that so far as Group IV corpuscles are concerned there is no abnormal blood elimination. The fact that Group IV corpuscles are not eliminated rules out the activity of any corpuscle poison during these periods. For in order to assume the activity of such a poison we will have to make it one that is not able to attack Group IV corpuscles, in which case the incidence of pernicious anemia should at least be lower among Group IV individuals than among others. In the 189 patients with pernicious anemia that have presented themselves at this Clinic during this study, 52 per cent were in Group IV, which happens to be a somewhat higher incidence than the occurrence of Group IV individuals found in general among our patients and donors. It must be that at the time when the patients were under observation there was no hemotoxin active. It has been argued that transfusion introduces something which neutralizes the hemotoxin. It does not seem probable that there would be a complete neutralization of the toxin and that the patient's symptoms would still persist. Although in some instances a remission was brought about by the transfusion, in most cases the patients returned for further transfusions after three months. Three months, it will be remembered, is the average length of duration of the presumably youngest Group IV transfused corpuscles in four pernicious anemia patients who were under observation to the end of elimination, and it is probably also the length of life of the like group transfusions. As in a few instances Group IV transfused blood stayed while the patient's total blood count dropped greatly, it would not seem that the protection of the Group IV corpuscles was due to an antibody to this hypothetical hemotoxin introduced by the transfused blood.

In the two cases (Cases 75 and 68) in which there was the most marked elimination, the Group IV transfusion was maintained and both the patients' corpuscles and the transfused like group corpuscles were eliminated. Since normal like corpuscles were eliminated, the elimination in these cases cannot be assumed to be due to any intrinsic weakness of the corpuscle. Since in this elimination there was a differentiation between like group corpuscles and Group IV corpuscles it would seem that the factor bringing it about must have been the result of an activity of the body itself.

This speeding up of the blood-destroying activity of the body, which seems to be the basis of the abnormal periods of blood destruction which are seen in transfused patients with pernicious anemia might be due, it is conceivable, to the effect of a toxin on the blood-destroying mechanism; or it might be due to some injury to the body, either past or present, which rendered the organism unable to elaborate the agents necessary to stabilize the normal physiologic blood-destroying process.

SUMMARY AND CONCLUSIONS OF PART II

Evidence is presented to show that there is no "hemolytic toxin" producing the anemia in pernicious anemia.

Partial evidence is presented to show that the periods of active blood destruction which are seen as the exception in cases of pernicious anemia during a series of transfusions are due to the activity of the blood-destroying organs of the body rather than to the intrinsic weakness of the blood corpuscle.

It is questionable whether blood destruction is as important a factor in producing the anemia of pernicious anemia as it is at present usually assumed to be.

THE EFFECT OF THE DIGESTIVE PERIOD AND OTHER FACTORS IN REACTIONS AFTER BLOOD TRANSFUSIONS*

JOHN L. BUTSCH AND WINIFRED M. ASHBY

Seven hundred thirty-seven transfusions were studied by the authors with the object of explaining the reaction to transfusions. The sodium citrate method, which is used routinely in the Mayo Clinic, was employed and uniform technic of observation carried out.

The cause of reactions was approached from the points of (1) technic, (2) factors intrinsic to the patient, and (3) factors involving both patient and donor.

It seemed possible that a small amount of hemolysis of the first few cubic centimeters drawn might take place and toxic product might be released. After about 50 c.c. of the blood had been run into the citrate solution, portions were centrifuged and the supernatant fluid observed for hemolysis. In the three cases showing hemolysis no connection was found between this and reaction to transfusion.

Omission of saline solution which had previously been used in transfusions gave no decrease in the number of reactions. It was, therefore, assumed that chills from the saline had not been common. The washing of all utensils in strictly neutral water gave no improvement in the percentage of reactions. Nor did the treatment of new rubber tubing, as recommended by Stokes and Busman, give results to indicate that this had been an important factor in producing the transfusion reactions. Desensitization of the patient was attempted by protracting the transfusion time to thirty minutes. In four patients thus treated there were two severe reactions.

Certain points regarding the condition of the patient were then observed. There was the least tendency to reaction when the initial temperature was normal and the tendency to reaction increased with increase in initial temperature. In 265 cases the hemoglobin percentages showed a definite relation to transfusion reactions, the lower percentages giving the greater number of reactions. In a series of eleven patients receiving from three to seven transfusions none developed hemolysis against like group corpuscles. Previous transfusions apparently have no desensitizing effect. The lower percentage reactions obtained in some instances in second and third transfusions in a series of eighty-four cases appeared to be due to factors, such as improved hemoglobin, temperature, and possibly blood volumes.

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* Abstract of paper published in full in the New York Medical Journal, 1922, cxiii, 513–517. From the Section on Medicine, Mayo Clinic, and the Department of Experimental Bacteriology, Mayo Foundation.

In studies on both patient and donor the slight possibility of intergroup agglutination was eliminated by 120 tests in which no evidence of agglutination was found. Precipitation tests in sixty-one cases were negative, nor was there evidence of any intrinsic compatibility or incompatability between a given patient and donor. The most interesting study, although the results were negative, was the effect of the digestive period on reaction. A certain proportion of patients and donors fasted previous to and following transfusion.

SPLENIC ANEMIA: A CLINICAL AND PATHOLOGIC STUDY OF SIXTY-NINE CASES*

WILLIAM C. CHANEY

Osler, in his "Principles and Practice of Medicine," discusses splenic anemia under the heading, "Primary splenomegaly with anemia," which he defines as "a primary disease of the spleen of unknown origin, characterized by progressive enlargement, attacks of anemia, a tendency to hemorrhage, and in some cases a secondary cirrhosis of the liver, with jaundice and ascites. That the spleen itself is the seat of the disease is shown by the fact that complete recovery follows its removal." Osler has included the cases of primary splenomegaly which Rolleston prefers to discuss under separate headings, "chronic splenic anemia" and "Banti's disease."

According to Rolleston, chronic splenic anemia presents the following characteristics: "(1) chronic splenomegaly which cannot be correlated with any recognized cause, (2) the absence of enlargement of the lymphatic glands, (3) chronic anemia (with low color index), (4) the absence of leukocytosis and usually the presence of leukopenia, (5) liability of copious gastro-intestinal hemorrhages from time to time, and (6) prolonged course without any tendency to spontaneous cure, though splenectomy is usually curative."

Rolleston, in discussing the relation between Banti's disease and splenic anemia, says, "The title, Banti's disease, is now often used as synomynous with splenic anemia even by those who fully recognize that it is a sequel or terminal stage of splenic anemia and does not occur in all cases even when unduly prolonged."

According to Hollins, Banti describes three stages of the disease named for him. First, is the pre-ascitic stage in which splenic enlargement is present with or without anemia. Second, is the transitional

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* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine, 1922. Reprinted from the American Journal of the Medical Sciences, 1923. Copyright by Lea & Febiger, Philadelphia. From the Section on Medicine, Mayo Clinic.

stage of which the most prominent symptom is diarrhea; anemia and blood changes are found, the liver is somewhat enlarged and jaundice may be present. Third, is the ascitic stage, or Banti's disease proper.

This report is the result of a study of the pathologic findings and clinical records of sixty-nine patients with splenic anemia, on whom splenectomy was performed at the Mayo Clinic from November 14, 1905 to September 1, 1920. Patients who had a distinct hepatic cirrhosis in addition are also considered.

THE MICROSCOPIC PATHOLOGY

Variation in the normal spleen.—Before the abnormality of any organ can be correctly investigated it is essential that the pathologist have a clear conception of the normal. This is especially true in the case of the spleen, for the gross and microscopic picture may vary widely under normal conditions. Such normal changes may be permanent or temporary, as in variations with age or after severe hemorrhage or sepsis. Before the pathologic study of splenic anemia was undertaken, therefore, an effort was made to learn of some of the variations that could be ascribed to normal influences.

Terminology.—By *sinus endothelium* is meant a specialized form of endothelium and not the lining cells of blood channels as the term is commonly employed. These specialized endothelial cells of the sinuses are probably reticular cells and to be correct should be so designated. The word *pulp* is used to designate the cellular structures lying between the sinuses. *Pulp cords* would probably have been a more suitable term. *Reticulum* refers to all the connective tissue not included in the capsule, trabeculæ, or blood vessels. Hyaline changes in the capsule and trabeculæ are not included under the term *degeneration*, which is reserved for degenerative changes in the reticulum, in the malpighian corpuscles, or within the pulp.

Method of study.—In order to express more accurately the degree of pathologic change observed in the study of the spleen, figures instead of descriptive adjectives have been used. Normal findings were marked marked zero or simply normal. The degree of increase of the various processes above normal was designated on a scale +1, +2, +3, +4, while the decrease was graded −1, −2, −3, −4; +5 and −5 have been used occasionally in grading very unusual and extreme conditions.

At least three blocks of tissue were taken from each spleen, one containing a portion of the capsule of the diaphragmatic surface, one from near the center of the organ, and one from near the hilus. The last block always included a portion of the wall of one of the large veins.

Microscopic sections were made by the frozen-section method or by embedding the tissue in paraffin. The routine stain was hematoxylin and eosin, but many of the specimens were also prepared with Dominici's and with methyl-green pyronin stains.

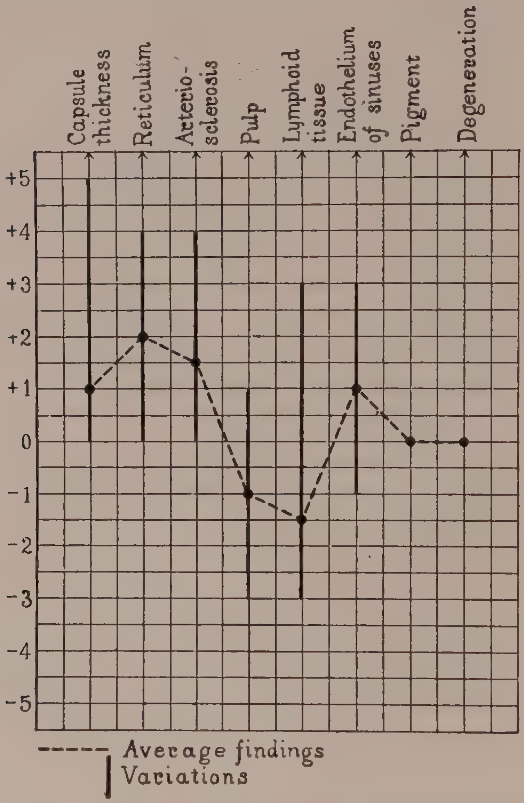

FIG. 146.—Average findings and the variations in the microscopic pathology of splenic anemia.

Microscopic findings.—A composite picture of the histopathology of splenic anemia is one of generalized fibrosis. There are no very definite and well defined characteristics which will enable the pathologist to say with certainty that the picture is one of splenic anemia (Fig. 146).

The wide variation in the pathologic findings in splenic anemia has been one of the arguments used in an attempt to prove that cases so classified belong in closely related clinical groups and do not bear a sufficient clinical and pathologic resemblance to justify their being considered as distinct disease entities. From the pathologic standpoint, in the case of the spleen, this argument is unfounded, for, while the pathologic variations are great, the microscopic and gross studies give results probably as characteristic of splenic anemia as similar studies in the other groups of splenomegaly that present an accepted clinical syndrome, such as pernicious anemia and hemolytic jaundice.

A great deal of the trouble in distinguishing, microscopically, splenic anemia from the other splenomegalies is owing to the variations encountered in the individual types of splenomegaly. In splenic anemia these variations were found to be quite marked. For example, the thickness of the capsule varied from normal to +5, the reticulum and the arterial walls from normal to +4, the pulp from −3 to +1, the lymphoid tissue from −3 to +3, and the endothelium of the sinuses from −1 to +3. While these variations are great, they are not surprising in view of the factors that may influence the spleen, such as the duration and severity of the disease, the age of the patient, and the changes that may have been caused by previous diseases. These variations, while confusing, nevertheless suggest that the spleen plays an important part in the vital economy of the individual.

The average thickness of the capsule was found to be +1. The variation from +3 to +5 was caused by the extensive hyaline plaques in some of the spleens. For the most part, however, the thickness of the capsule in any given specimen was uniform. As a rule, the more fibrous the capsule, the more prominent were the trabeculæ throughout the splenic tissue. Lymphocytic infiltration of the capsule was not seen in any of the sections.

The reticulum may be distinctly prominent either because of marked fibrosis or great cellular activity. The degree of fibrosis of the reticulum seemed to vary in a slight degree with the amount of thickening of the vessel walls, yet many cases were found in which the reticulum was very cellular and the degree of arteriosclerosis marked. The amount of lymphoid tissue present usually varied inversely to the prominence of the reticulum. The average amount of reticulum was found to be +2.

In the study of the degree of arteriosclerosis the artery of the malpighian corpuscle was chosen. It was observed that the more marked the arteriosclerosis, the greater the tortuosity of the vessel, so that it was often found that a malpighian corpuscle might show two to four cross-sections of the same artery. Marked arteriosclerosis was not necessarily associated with extensive fibrosis, and no evidence was found to suggest that fibrosis developed from the vessel wall. Indeed, marked fibrosis was often found in which the fibrous tissue was conspicuously absent in the region of the malpighian corpuscle and the central artery. Arteriosclerosis was, to a slight degree, an exception to the rule that in any given spleen the pathologic changes were uniformly distributed. A few spleens showed a variation of from +1 to +3 in the degree of arteriosclerosis in various sections of the organ.

The artery of the malpighian corpuscle was in almost every case eccentrically located, and its position was apparently not disturbed by the thickening process of the vessel wall. There seemed to be at least one factor which helped to determine the size of the malpighian corpuscles, that is, encroaching fibrosis. The fibrosis, in turn, seemed to affect the position of the central artery by reducing, in an irregular fashion, the size of the malpighian corpuscle. It was a fairly constant finding that the greater the fibrosis, the more eccentrically located was the artery. The average degree of arteriosclerosis was +1.5.

The degree of thickening of the arterial walls in cases of splenic anemia and in other types of splenomegaly were, syphilis +3, hemolytic jaundice +3, pernicious anemia +2, myelogenous leukemia +2, and splenic anemia +1.5.

No marked abnormality could be detected in the splenic veins, but the veins were usually so closely associated with the trabeculæ that a comparison of their walls was very difficult. In many cases, however, distinct hyaline changes were seen in the walls of the veins, but in no specimen was thrombophlebitis present.

In a spleen in which generalized fibrosis is a prominent feature it would naturally be supposed that the amount of splenic pulp would be decreased. This was found to be true, and the average was −1. In general, the amount of splenic pulp varied inversely to the degree of fibrosis and the prominence of the sinuses. The proliferative activity of the endothelium of the sinuses, or the true reticular cells, was above normal and was rated +1. In nearly all the microscopic specimens the sinuses were prominent and dilated, but the other types of splenomegaly also showed it. The syphilitic spleens especially resembled those of splenic anemia in this particular. The prominence of the sinuses in splenic anemia averaged approximately +2.

The sinus endothelium or reticulum showed varying degrees of proliferation. In some specimens the cells seemed especially inactive, while in others the cells were very large and, as further evidence of activity, were free within the sinuses.

Downey, in an unpublished article, "The structure and origin of lymph sinuses of mammalian lymph nodes" makes some very interesting statements: "Both the embryological and anatomical studies have shown, therefore, that the tissue of the splenic sinuses is to be regarded as reticulum rather than endothelium. . . . It is not identical with the endothelium of blood and lymph vessels." With regard to the relation of the reticular tissue to the sinuses, he says, "The sinuses are closely associated with the reticular tissue of the organs concerned."

The amount of lymphoid tissue was found in many cases to be markedly below normal, but the average was estimated at −1.5. In determining the amount present in any given microscopic specimen the malpighian corpuscles, perivascular lymphocytic infiltration, and the lymphocytes generally distributed throughout were considered. As a rule, the malpighian corpuscles were fairly well defined and small, but they did not stand out prominently nor were they seen often. Contrary to the findings of certain observers, in this series the so-called germinal centers were very rarely seen and, when found, were small and inconspicuous. The intermediate zone of the malpighian corpuscle, "the zone of expansion," which in normal splenic tissue stains deeply and is prominent, was poorly defined and scarcely noticeable.

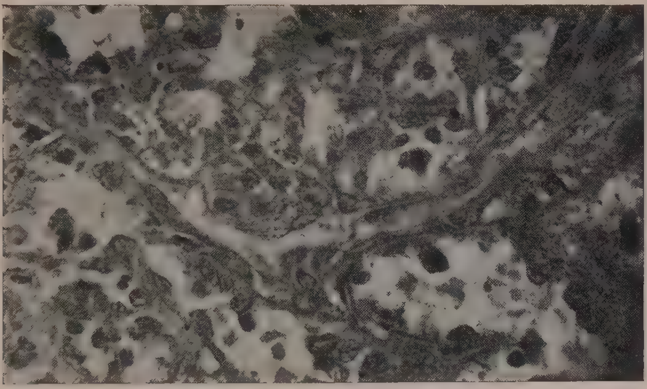

FIG. 147.—Splenic anemia; a capillary is seen.

An attempt was made to study the minute capillaries which are connected with the splenic sinuses (Figs. 147 and 148). In normal splenic tissue these small blood channels consist of but a single layer of endothelial cells, the media and the adventitia disappearing as the vessel approaches the size of a capillary. In splenic anemia and in the other splenomegalies, the spleens showed an increase of fibrous tissue around these vessel walls. Due allowance, however, must be made for the fact that the venous capillaries enter the trabeculæ soon after their formation. In many instances the walls of these vessels showed a decided hyaline change so that the lumen became quite small and irregular.

In attempting to make a differential diagnosis of the various groups of splenomegaly the greatest difficulty was experienced with syphilitic spleens which resembled those of splenic anemia very closely. The sinuses in the syphilitic spleens were as prominent as those in the spleens of splenic anemia and the fibrosis was as great.

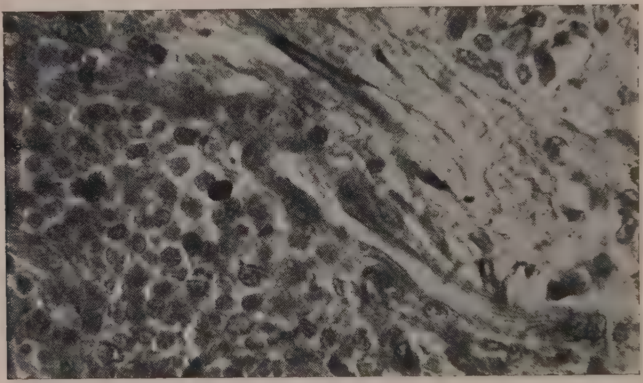

Fig. 148.—Splenic anemia; small capillary near a trabeculum.

On account of the relative prominence of the malpighian corpuscles and the accuracy with which they can be studied they were given special consideration, particularly from the standpoint of relative size and number, and general structure. While the malpighian bodies of splenic anemia were fairly prominent in the microscopic specimen, and were well circumscribed, they were not so prominent as in the normal, or in cases of pernicious anemia. There were only two or three specimens, however, in which the boundaries of the corpuscles could not be marked out with a fair degree of accuracy.

Contrary to many reports on the subject of splenic anemia, areas of degeneration or fibrous nodules were not found within the malpighian corpuscles. This, however, is entirely in accord with the ideas of Cushing and MacCallum who, in discussing splenic anemia, said, "No progressive sclerotic process, such as Banti described, is seen in these malpighian bodies, nor has it been possible to find any fibrous nodules which might have resulted from such a sclerosis."

The larger the malpighian corpuscle, the greater was its tendency to be round or oval in shape and the nearer the center the artery seemed to be. As the generalized fibrosis increased in amount the malpighian corpuscles became smaller and were more irregular in outline.

As the fibrous tissue encroached on the periphery of the malpighian body, it seemed to cut off groups of cells somewhat irregularly. A continuance of this process resulted many times in the malpighian body being composed of a group of cells without a perceptible central artery, the vessel lying entirely outside of the corpuscle.

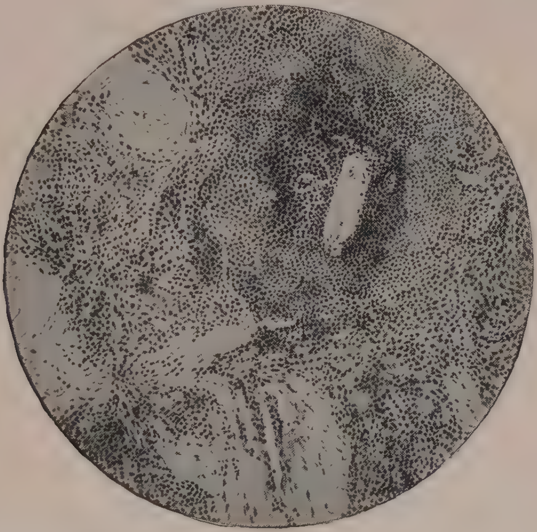

FIG. 149.—A malpighian corpuscle with a great amount of fibrosis around it. The central artery is cut obliquely.

Before discussing the size of the malpighian body in splenic anemia the size of the normal should be considered. Gray gives the size of the malpighian corpuscles of the spleen as varying from 0.25 to 1 mm. in diameter. Morris gives the average size of the normal as 0.25 to 1.5 mm. Mall says the splenic lobule in a normal spleen is about 1 mm. in diameter and adds, "The malpighian corpuscle usually lies in the proximal end of the lobule, but in case it is very large it may distend the lobule and cause it to bulge."

In order to determine the size of the malpighian corpuscle in splenic anemia a camera lucida was used with the low power of the microscope (Fig. 149). Most of the corpuscles were not exactly round and for this reason the length and breadth were measured and the average was taken. When due allowance had been made for the magnification, it was found that the average size of the malpighian corpuscle was approximately 0.35 mm. in diameter. The variation in size was from 0.2 mm. to 0.6 mm. It is evident, therefore, that the size of the corpuscles in splenic anemia is within the limits of normal, but that the average size is much below the average in the normal.

The next step was the determination of the number of malpighian bodies in a given area of splenic tissue in splenic anemia. The dissecting microscope proved to be very helpful in this work. A square 0.5 by 0.5 cm. was the size of the field chosen and three fields were counted in each spleen in order to get a general average of different portions of the organ. After determining the average for each spleen, the average for sixty-nine spleens was found. The average number of malpighian bodies for each 0.5 cm. squared, or for one-fourth of 1 square centimeter, was found to be nearly 6. The number of malpighian bodies in a square centimeter was estimated as approximately 23. Certainly this number is far less than the number of malpighian corpuscles in the same area in a normal spleen. In a series of about twelve normal spleens (far too few for calculating accurate averages), the number of malpighian bodies for each square centimeter was approximately 40.

The relation of the number of malpighian bodies to the size and weight of the spleens furnishes interesting data. As in all statements concerning the pathology of splenic anemia, however, there are many exceptions. The number of malpighian corpuscles to each square area seemed to decrease as the size and weight of the spleen increased. The size of the malpighian body became smaller as the weight and size of the spleen increased. This was found to be true in 70 per cent of the spleens, and would seem to indicate that the number of malpighian corpuscles in a spleen remains constant until a fibrotic or some other pathologic process becomes so marked that many of the corpuscles are completely destroyed or are made so small that they are not recognized.

GROSS PATHOLOGY

As in the microscopic study, a consideration of the gross pathology consisted in the study of the sixty-nine spleens of splenic anemia and a comparison with 175 specimens from the various other groups of splenomegaly.

The average weight of these spleens was approximately 950 gm., and the variations in weight 120 to 2,290 gm. If patients less than ten years of age were excluded, the average weight increased to 1,015 gm. Rolleston found the average weight in twenty-one cases of splenic anemia to be 782.46 gm.

When the average weight of these spleens was compared with that of the other groups of spleens of splenomegaly it was found that those of Gaucher's disease and those in the lymphoma group averaged higher in weight. The spleens arranged according to their number and average weights were: Gaucher's disease, four, 3,031 gm.; the lymphoma group, five, 2,249 gm.; splenic anemia, sixty-nine, 1,015 gm.; pernicious anemia, fifty-three, 940 gm.; myelogenous leukemia, twenty-six, 937 gm.; hemolytic jaundice, thirty-two, 920 gm.; syphilis, six, 778 gm., and tuberculosis, four, 501 gm. It must be borne in mind that all of the spleens here considered were obtained at operation.

An effort was made to ascertain if the weight or size of the spleens varied in any other pathologic conditions. Curves were made in order that any slight variation might be detected. When compared with the weight and size there was no constant change found in the thickness of the capsule in the reticulum, in arteriosclerosis, or in the pulp or endothelium of the sinuses. The heavier spleens showed a slight tendency to have thicker capsules or a greater degree of perisplenitis. The spleen of splenic anemia maintained to a rather remarkable degree the shape of a normal spleen. From the standpoint of perisplenitis, the average was found to be +2. Thirty-eight were +2, eighteen +1, nine +3, and four +4.

Only five spleens showed macroscopic infarcts and these were variable in size, the largest being 12 by 8 by 3 cm. and the smallest scarcely perceptible. In these five specimens the average arteriosclerosis was +1.2. In three cases there was a history of abdominal pain and in three of gastric hemorrhage. In three cases also, ascites was present. All the changes mentioned, arteriosclerosis, pain, hemorrhage, and ascites were present in one case only. There was no constant clinical or pathologic finding in the spleen in any of the cases of infarct.

A typical spleen of splenic anemia bears the general shape of a normal spleen, but is about five times as large. When allowed to rest on the table it maintains its shape much better than the normal spleen which flattens out; it is several times as firm as the normal. Its capsule is grayish white with a slight reddish or a purplish red tint. Hyaline plaques may or may not be seen on its surface; in the average spleen they would not be present. Perisplenitis is very evident, especially on the diaphragmatic surface.

The typical spleen of splenic anemia offers considerable resistance to cutting. The cut surfaces bulge outward and present a red, beefy appearance. Fibrosis is very evident, and the trabeculæ are especially prominent. The malpighian bodies are not seen. The cut surface of a specimen that has been preserved in formalin is quite pink and the trabeculæ, which have become very white, form a prominent network over the surface.

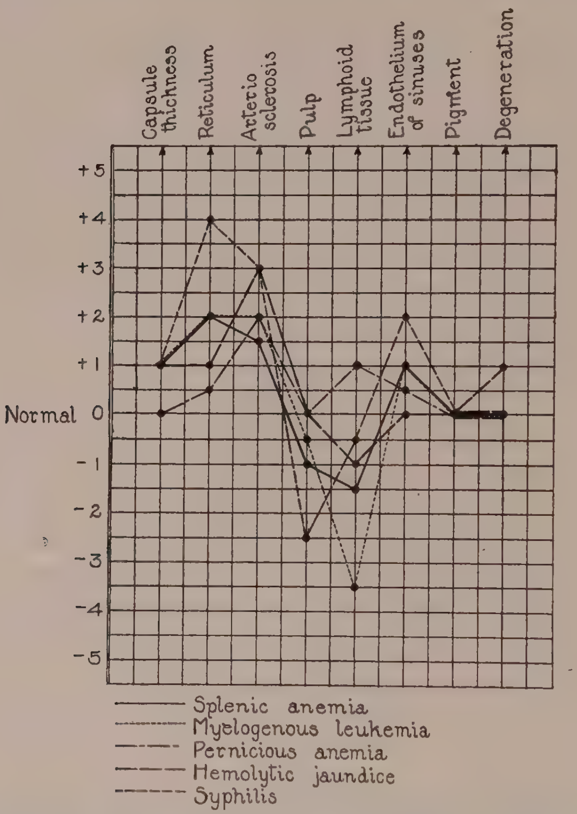

FIG. 150.—Microscopic pathologic findings in splenic anemia, myelogenous leukemia, pernicious anemia, hemolytic jaundice, and syphilis.

When the results of the pathologic study of splenic anemia are summarized and the findings are compared with a similar study of the other groups of splenomegaly, such as pernicious anemia, leukemia, and hemolytic jaundice, the general impression obtained is that there is a very great pathologic variation within each group and that while certain conditions seem to be more common in some groups than in others, the findings overlap, to a great extent. The points of similarity in the various groups are rather striking and suggest that the spleen may play a similar part in all of the diseases that produce splenomegaly (Fig. 150).

CLINICAL FINDINGS

The sixty-nine patients with splenic anemia had been in poor health for an average period of seven years when they came to the Mayo Clinic. Because of the insidious onset of splenic anemia and the unreliability of the patient's memory, the possibility of inaccuracy in this statement is, of course, very great. Moreover, seven years does not indicate the entire duration of the disease, but the period of illness previous to the time of splenectomy.

The average age of the patients was thirty-three years, the youngest being two and one-half years, and the oldest sixty-nine. If the average age is thirty-three years and the average duration seven years, the onset must have been at about the age of twenty-six. The duration of the illness was in all probability more than seven years, for many of the patients gave a history of "always being delicate." They dated the onset of their illness, however, from the time of some marked disturbance, such as a gastric hemorrhage. The distribution was about equal in the sexes, there being thirty-six male patients and thirty-three female.

In no instance was a history of injury obtained as a possible cause, nor did the records show an instance of two or more cases of anemia occurring in the same family. Occupation was apparently not a factor.

Most of the patients complained of more than one abnormal condition which they considered of great importance in their illness. The complaints may be summarized as follows: enlarged spleen and mass in left abdomen, twenty-nine; hemorrhages from the stomach, twenty; and weakness, nineteen. Indigestion, pain in the left side of the abdomen, and anemia were each complained of in six cases. Diarrhea was mentioned in three, pallor in three, pain in epigastrium in two, shortness of breath in two, and jaundice in two; while rheumatism, constipation, palpitation, headaches, bleeding from the bowels, pain and numbness in legs, nervousness, and asthma were each mentioned but once.

The frequency with which hemorrhage occurred was rather surprising. It was not only a very common complaint, but often the severity of it was so alarming that it was a common cause for seeking medical attention. The histories showed that forty-one of the sixty-nine patients had hemorrhages. Thirty-eight of these were recognized by the patients as having come from the stomach as they had vomited blood, and twenty-seven, besides the vomiting of blood, had recognized blood passed by the bowel. Of the three remaining patients one noticed blood in the bowel movements only, and two had quite profuse nasal bleeding. From the standpoint of severity, these hemorrhages may be graded 1, 2, 3, and 4. In five patients bleeding was graded 1, in eighteen, 2, in seventeen, 3, and in one, 4. Many of the patients spoke of the alarming nature of the hemorrhages; their prostation was so great that they had to remain in bed from three days to two weeks.

Abdominal pain was rarely mentioned as the chief complaint; probably its relative infrequency caused the patient to consider it of minor importance in his trouble. Nevertheless, on being questioned, thirty-two patients told of having had one or more attacks of pain, most of which were short, but often rather severe. Four of these patients located the pain definitely over the spleen. Two had midepigastric pain, while one located the painful area in the lower right quadrant. There were twenty-five, therefore, who were indefinite with regard to the site of the pain. According to Giffin, "Pain in the region of the spleen in splenic anemia is common and is probably due to perisplenitis which is so often present." Certain patients who complained of pain in the left abdominal area while under observation, presented definite friction rubs over the spleen.

Evidence was found elsewhere than in the spleen that might explain the pain in fifteen of the thirty-two patients who had had pain. Six of those who complained of abdominal pain and one of midepigastric pain had gallstones; four with abdominal pain had diseased gallbladders and four had chronic appendicitis.

Eight patients gave histories of having had malaria. None of these had had recent attacks nor had the disease lasted long. In all of them a special search had been made in the blood smears for the malarial plasmodium with negative results. Some investigators have taken exception to Banti's cases because they came from malarial districts.

Geographical distribution of the patients in this series was: Minnesota fourteen, Iowa eight, Wisconsin six, South Dakota six, Illinois five, Canada five, Montana, North Dakota, Nebraska, Michigan, Missouri, and Texas each two, and one each from Oregon, Indiana, Wyoming, New Mexico, New York, Pennsylvania, West Virginia, Kentucky, Tennessee, Mississippi, Alabama, and Arkansas.

Usually the first note made by the clinician in his physical examination was the size of the spleen. There was only one patient whose spleen could not be palpated and this might be explained by the presence of ascites; the spleen in this case weighed 390 gm. In two patients whose spleens could just be felt below the costal margin, the organs weighed 250 gm. and 425 gm. Another spleen, felt rather indistinctly and described as "a mass in the splenic region," weighed 318 gm. A spleen of 530 gm. was designated as "one inch below the costal margin." On nearly every history chart a drawing was made by the examiner to show what he considered the relative size of the spleen. The size thus roughly designated varied in a general way with the weight in all except two instances. In these exceptions a spleen of 120 gm. and one of 320 gm. were outlined to suggest a much greater size. Judging from the diagrams on these histories a spleen that extended to the middle line and down to about the level of the umbilicus should weigh approximately 1,000 gm. It would seem that the spleen maintained its relative position in the abdomen in spite of the enlarging process.

The adhesions around the spleen were so marked that special mention was made of them in thirty-three cases. There were, however, few spleens with elongated pedicles. On only one surgical card was reference made to the presence of a twisted pedicle. The spleen in one patient who had never had hemorrhages showed one complete turn; the organ weighed 610 gm.

In the physical examination the feel of the spleen was generally described by the clinician as "hard and smooth." A notch was felt in approximately 50 per cent.

Notes in the physical examinations regarding the size of the liver referred to twenty-four as enlarged. Some of these organs, however, were apparently just below the costal margin and were marked "questionable enlargement." According to the operative findings, there were twenty-six patients who had enlarged livers. At operation thirty patients were found to have definite cirrhosis of the liver and in only thirteen of these, was the liver larger than normal. The average weight of the spleen in the twenty-four cases in which the liver was described as enlarged was found to be 1,016 gm.

Presumably the size of the liver in splenic anemia bears no close relationship to the size and weight of the spleen. The findings in this series of cases suggest that there is a steady progressive enlargement of the spleen, but that the liver maintains its normal size until relatively late in the course of the disease. It then enlarges and may remain enlarged, or it may return to its normal size or become even smaller than normal. It cannot be said just how early in the disease cirrhosis of the liver begins. In many respects, therefore, the physical findings in splenic anemia are the reverse of those in portal cirrhosis, for in this latter disease a palpable spleen is usually found relatively late.

Ascites was present in twenty-four patients, twenty-three of whom had cirrhosis of the liver. In the other case the liver was enlarged, but apparently not cirrhotic. Allbutt and Rolleston are of the opinion that in splenic anemia ascites may occur in the absence of hepatic cirrhosis.

Only very general statements can be made with regard to weight lost during the progress of the disease. In most cases the disease had lasted so long that the patient was uncertain as to his weight before onset. It would seem, however, that in a series of twenty-two cases the average loss of weight was only five pounds. The greatest loss was twenty-seven pounds, and three patients weighed more than what they considered their normal.

Bronzing of the skin is often mentioned in splenic anemia. In this series twenty-one patients were described as sallow or pale; twelve showed yellowness of the skin; seven were described as lemon yellow; five, brownish yellow; one, tanned skin; one, cachectic looking, and one, brownish pigment about the eyes. Twenty-seven, then, showed some change in the color of the skin. Twenty-one of the remaining forty-two patients showed sufficient pallor to attract attention. None of the patients appeared to have definite icterus.

In none of the histories was there a note concerning any enlargement of peripheral veins of the abdomen or chest.

From the standpoint of the laboratory work the blood count was undoubtedly the most valuable, but the reports on the coagulation time, fragility test, Wassermann reaction, and stool tests were not without value. Blood counts were made on all patients with splenic anemia before splenectomy, and on most of them at varying times after the operation.

The Wassermann test was done in sixty instances and was negative in fifty-nine. The one positive reaction was later discredited as a result of four subsequent negative tests. Four patients gave a history of syphilitic infection, but in none of these could evidence of syphilis be found.

Stool examinations were seldom made. There were apparently two indications: a history of diarrheal attacks, or of residence in the tropics. Thirteen stool examinations were done, with the following results: nine were negative; two showed *Amœba histolytica;* one, *Lamblia intestinalis*, and one, circomonads and trichomonas. None of the patients, however, had diarrheal attacks.

The fragility test was made in twenty-nine of the patients. In fifteen of these the fragility was normal; only one showed a tendency towards an increase in fragility of the corpuscles, while thirteen showed an increased resistance.

The coagulation time was determined in only thirteen patients. All except one were between two and ten minutes. One patient showed a coagulation time of fifteen minutes. In this determination either the Biffi-Brooks coagulometer, the Boggs coagulometer, or the Lee and Vincent test tube method was employed.

A study of the relation between the number of erythrocytes and leukocytes and the hemoglobin before operation revealed a varying degree of anemia. In every case this was of the secondary type, the color index in many cases being relatively low. There was always a relative leukopenia and in some of the counts the number of leukocytes was low in comparison to the number of red corpuscles. The average erythrocyte count was 3,700,000, the hemoglobin 53 per cent, and the leukocytes 4,900. In the thirty patients with definite cirrhosis of the liver the erythrocytes were about 3,500,000, the hemoglobin 50 per cent, and the leukocytes 4,600. In the thirteen patients with enlargement of the liver, but without definite cirrhosis, the erythrocytes were about 4,000,000, the hemoglobin 56 per cent, and the leukocytes 5,800. The remaining twenty-six patients who had approximately normal livers had an average erythrocyte count of 3,750,000, hemoglobin of 55 per cent, and a leukocyte count of 5,000.

In many of the patients changes in the erythrocytes were noted and were usually designated as slight or moderate. These changes were seen in patients with the greatest degree of anemia. Poikilocytosis and anisocystosis were noted in twenty-nine of the sixty-nine patients; anisocytosis, poikilocytosis, and normoblasts in twelve; and anisocytosis alone in nine. Only occasionally mention was made of polychromatophilia.

In most of the patients blood counts were made at varying intervals after splenectomy and in every case there was a marked increase in the number of leukocytes. The normal was taken as 8,000, and in each case the number of days after operation was considered. A composite chart showed that there was an initial rise in the leukocytes immediately after the operation and that the number gradually increased until about the forty-fifth day. There was then a gradual decrease until the count approached the normal line in seventy-five to one hundred days after splenectomy. An abrupt rise occurred previous to the tenth day after splenectomy. From the tenth day to the thirtieth the increase was more gradual. A very gradual decrease then followed until the normal line was approached.

An attempt was made to determine how long secondary anemia persisted after splenectomy, but the results were rather inconclusive. It is certain, however, that there was an improvement in the hemoglobin and the number of erythrocytes. The degree of improvement varied greatly, so that no time relation could be established. In only a very few cases were two or more blood counts made following splenectomy and, while these showed progressive improvement, the number was too small from which to draw conclusions.

A differential cell count was made in sixty-three of the patients before operation. In the remaining histories the count was noted as normal, and so had to be discarded. If the normal number of polynuclears be considered as varying between 60 and 70 per cent (Piersol) the preoperative counts in these cases were normal in twenty-four cases, below normal in ten, and there was a relative increase in twenty-nine. According to Pappenheim the number of lymphocytes found in a normal differential count is from 20 to 22 per cent. When the lymphocyte counts were compared with these standard figures it was found that ten were within the limits of normal, thirty above normal, and twenty-five below normal. A comparison was next made between the preoperative and postoperative differential counts. In thirty-five patients one of the differential counts had been omitted. Postoperatively ten patients showed an increase in the polynuclears, and twenty-two showed an increase in the relative number of lymphocytes. Two patients showed practically no changes in the blood following operation. The length of time that elapsed after splenectomy seemed not to have been an important factor. In patients with an increase in the polynuclear cells, however, the differential count had been made from seven to forty-three days after operation.

Most of the operative findings have already been discussed, but the condition of the gallbladder as found at operation has only been considered in part. In eleven cases it was described as diseased, markedly distended, or as having a thick wall. In eight patients the gallbladder contained stones.

The vermiform appendix was diseased in seven patients and the extent of disease was +2 or +3.

PATIENTS WITH CIRRHOSIS OF THE LIVER

There is considerable confusion in the literature with regard to the relation between Banti's disease and splenic anemia. Most American writers choose to consider the two as entirely synonymous, while foreign authors prefer to make a well marked distinction between them.

MacCarty, of the Mayo Clinic, has examined specimens of hepatic tissue obtained at operation in nearly all of the sixty-nine cases of splenic anemia here reported, and he is of the opinion that in none of them, no matter how short the duration of the disease, was the liver entirely normal. From the mildest case to the most severe the liver showed varying degrees of hepatitis. In the more severe types periportal fibrosis was evident, but there was no sharp line of distinction between those with well defined cirrhosis and those without.

Thirty cases in which there was definite evidence of portal cirrhosis have been grouped together. From the standpoint of morbid anatomy these thirty spleens very closely resembled the remaining thirty-nine. Their average weight was a little greater, being 1,027 gm. as compared to 1,015 gm. of the entire series. There was a slight increase in the amount of fibrosis, but in all other respects no difference could be made out.

This close similarity was found also in the microscopic study. Each pathologic finding was graded and averaged as in all the other cases and the results were expressed in a curve. This curve was found to correspond exactly with that for splenic anemia, except that the splenic pulp was −1.4 instead of −1.

The clinical study of this group showed interesting variations from the entire series of cases. The average age was thirty-five; duration of disease was nine years. As in the other cases, most of the patients dated the origin of the disease not from the time of the real onset, but probably from the time of some severe manifestation, such as gastric hemorrhage. Nineteen of these patients gave a history of hemorrhage, the severity of which was no greater than that of the remaining twenty-two patients who also complained of hemorrhages. Eighteen had gastric hemorrhages, fourteen had also noticed blood passed by the bowels, and one had nasal bleeding; one complained of melena only.

In the chief complaints hemorrhages were mentioned eleven times, while enlarged spleen and abdominal mass, if considered together, were complained of twelve times. The less important complaints, in order of frequency, were stomach trouble, five; anemia, four; abdominal pain, four; weakness, four; jaundice, two; dyspnea, one; constipation, one, and pain in the legs, one.

While most writers consider true Banti's disease to include all patients with definite cirrhosis of the liver, according to Banti there should be ascites besides the cirrhosis. Ascites was rather common in this group, being noted in twenty-four patients who could, therefore, be classified as cases of true Banti's disease. In ten of these it was sufficiently marked to be noticed before operation. Thirteen of the thirty patients had enlargement of the liver. An effort was made to find some difference between the twenty-four cases which showed ascites and the remaining six cases of the cirrhosis group. Practically no difference could be made out, and for this reason a separate discussion of the group of true Banti's disease would be but a repetition of that given on the group of patients with decided cirrhosis of the liver.

A comparison of the postoperative mortality in patients with cirrhotic livers with that of the remaining patients was interesting. In the sixty-nine patients the highest mortality occurred within forty days of the operation; twelve had died within this period, and seven of these were patients with marked cirrhosis. If these figures are expressed in terms of percentage, it is seen that 23.3 per cent of the patients in the group with cirrhosis died within forty days of the operation, while only 12.8 per cent of the other patients died within the same length of time.

In splenic anemia the condition seems to be one of underfunction of the spleen rather than of overfunction. In the conflict with disease, while all the body tissues suffer, the spleen seems to bear the brunt of the battle. As the normal tissue of the spleen is destroyed it is replaced by fibrous tissue and the organ enlarges in an attempt to keep up its struggle against the disease. Finally, the spleen decompensates and, instead of being a help, it becomes a menace and may be a focus from which the disease is better able to attack the liver and the other organs.

This suggests the question of the most advisable time to perform splenectomy in cases of splenic anemia. From the standpoint of the operative mortality alone the spleen should certainly be removed before definite hepatic cirrhosis has occurred. In the future the development of some test of hepatic function may indirectly be an index to the functional activity of the spleen.

THE MORTALITY AND THE POST-MORTEM REPORTS

A general summary of the deaths in this series of patients with splenic anemia has been given by Giffin. There were nine deaths in hospital and six of these patients showed a definite cirrhosis of the liver. It would seem, therefore, that cirrhosis of the liver, especially if associated with ascites, is a very great factor in increasing the operative risk in this disease.

SUMMARY

1. A composite picture of the pathologic findings in the spleen in splenic anemia was found to be one of generalized fibrosis. There were no findings in the splenic tissue that would enable the pathologist to make a positive diagnosis of splenic anemia, yet the abnormality was as characteristic of this disease as in other diseases producing splenomegaly.

2. The degree of fibrosis of the reticulum seemed to vary in a slight degree with the amount of arteriosclerosis. There was no evidence to show, however, that this fibrosis originated in or around the vessel walls.

3. The size of the malpighian corpuscle seemed to be affected by the degree of fibrosis, and the greater the fibrosis, the more eccentric was the so-called central artery.

4. The splenic veins presented no marked abnormality or evidence of thrombophlebitis.

5. Dilatation of the sinuses was fairly constant and the reticular cells showed a proliferative activity. The syphilitic spleens resembled those of splenic anemia in this respect.

6. The amount of lymphoid tissue present was usually below normal. The malpighian corpuscles were fairly well defined, but the so-called germinal centers were small and seldom seen. Areas of degeneration or fibrous nodules were not found in the malpighian bodies.

7. As a result of an actual measurement it was found that the size of the malpighian corpuscles was within the limits of normal, but that the average size was below the average for the normal. The number of corpuscles for each square centimeter was found to be twenty-three.

8. By actual figures 70 per cent of the spleens showed that the number of malpighian bodies for each square area decreased and the size of the corpuscles became smaller as the size and the weight of the spleen increased.

9. The average weight of the spleens was found to be 1,015 gm.

10. The average age of the patients with splenic anemia was thirty-three years, and the number of males was about equal to the number of females. There was apparently no familial tendency.

11. The most common complaints were mass in the left abdomen, gastric hemorrhage, and weakness.

12. While abdominal pain was rarely given as the chief complaint, the histories brought out the fact that thirty-two of the patients had attacks at some stage of the disease. In many instances the pain was probably due to perisplenitis.

13. In the physical examination spleens designated as just palpable weighed from 250 to 500 gm., while spleens of approximately 1,000 gm. extended to the middle line and almost to the level of the umbilicus.

14. The relation of the size of the spleen, as given by the clinical records, to the actual weight, and the fact that many adhesions were found at operation, suggested that the spleen of splenic anemia maintains its relatively normal position in the abdomen.

15. Physical examination showed twenty-four enlarged livers, while at the operating table twenty-six showed a definite cirrhosis, and thirteen were larger than normal. The size of the liver seemed to have no relation to the size and weight of the spleen.

16. In the sixty-nine patients the average erythrocyte count was 3,700,000, the hemoglobin 53 per cent, and the leukocyte count, 4,990. The coagulation time and the fragility test were normal, and the Wassermann tests and the stool examinations were negative.

17. A composite chart of the blood counts made after the operations showed a gradual increase in the leukocytes up to the forty-fifth day. There was then a gradual decrease until the normal was reached in about seventy-five days. A similar result was obtained in a composite chart in which the number of leukocytes found in the counts made before the operation was taken into consideration.

18. A comparison of the number of lymphocytes in the differential count showed that the average was within the limits of normal. A lymphocytosis did not seem to be a characteristic in this series.

19. In the study of the liver tissue in the cases of splenic anemia, thirty showed a definite cirrhosis, but in none was the liver entirely normal.

20. The chief complaints of the thirty patients that have hepatic cirrhosis were the same as those in the rest of the series; hemorrhage and abdominal mass were the predominating complaints.

21. Twenty-four of the patients with cirrhosis of the liver had ascites.

22. Twenty-three and three-tenths per cent of the patients with cirrhotic livers died within forty days of the operation, while within the same length of time the death rate of the remaining patient was only 12.8 per cent.

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CHANGES IN THE MORPHOLOGY AND FUNCTION OF THE BONE MARROW AFTER SPLENECTOMY*

ERNEST M. JOHNSTONE

INTRODUCTION

In this series of investigations on the bone marrow I have had a two-fold purpose; first, to devise a new method of studying marrow that would secure a connected picture of changes in the marrow, and second, to observe the function of the marrow after the removal of the spleen. The need of this investigation was suggested to me by my findings in a previous study of the blood changes after removal of the spleen for kala azar.

Hitherto most observations on the function of the marrow have been limited to single isolated specimens, usually secured at necropsy or by etherizing laboratory animals. A single specimen of bone marrow is insufficient evidence. An adequate conception of the behavior of the marrow can be secured only by frequent observations (on the same person or laboratory animal) at regular intervals and over a period sufficiently long to afford a connected record of changes throughout the entire course of the disease. One of the most difficult factors in connection with the technic is adequate experimental control. I have, therefore, given special attention to the development of a system of rigid experimental control.

It should be stated that my reason for undertaking this study of the marrow and for giving special attention to the early period after splenectomy is the fact that previous investigators, notably Pearce and Krumbhaar, have reported practically negative findings for the first six months. They noted definite marrow changes, however, after from six months to one and one-half years. Their study of the marrow after splenectomy still constitutes the most complete contribution on the subject.

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The fact that the most severe stage of anemia and most instances of recovery therefrom occur during the first six months after the removal of the spleen naturally leads us to expect corresponding marrow changes during this period. Pearce and Krumbhaar, failing to find such marrow changes during the first six months, concluded that the changes observed later could not be considered compensatory to an anemia which had already cleared up. They stated their reasoning thus:

"If the hyperplasia of the bone marrow is compensatory to increased blood destruction or decreased blood formation one would expect definite hyperplasia during the earlier period, during the first three months after splenectomy at a time when the anemia is evident and repair is taking place, and not six months to a year and a year and a half when the blood picture is normal; . . . it is therefore impossible, on account of the late development of the hyperplasia of the marrow, to explain its occurrence as compensatory to the anemia following splenectomy."

Contrary to these observations by Pearce and Krumbhaar and their associates, my study of marrow changes after splenectomy has shown definite early changes. The differences in our findings are, I believe, due to variations in methods. First, there is a fundamental difference in the method of experimental control. They used the marrow of one animal to control changes in another animal, whereas, I controlled postsplenectomy changes by a control specimen of marrow taken from the same animal before splenectomy. I also studied a series of non-splenectomized animals subjected to exactly the same conditions as a subsidiary control. Second, it is important to note that Pearce and Krumbhaar and their associates made no observations during the fourth and fifth months after splenectomy. This is significant because it was during these months that I observed maximal marrow changes. Third, my method accomplished a connected picture of marrow changes not possible by the study of single and isolated specimens of marrow taken from various animals. Fourth, in my method the rib marrow was studied instead of the marrow of the central third of the femur. The rib marrow shows marrow changes earlier than the marrow of the central third of the femur.

It is evident that the function of the marrow during the first few months after splenectomy is the crux of the problem. If during this period there is hyperplasia and hyperactivity, postsplenectomy anemia is due to no fault of the marrow but, rather, to some destructive factor, possibly an hemolysin, which is set into activity by removal of the spleen. Since the question of the function of the marrow, especially during the period immediately following splenectomy, is of sufficient importance to warrant further investigation, I have ventured to continue the study of the problem by devising a new method and by giving more emphasis to the accomplishment of rigid experimental control.

EXPERIMENTS

The schedule for this investigation of the marrow and its relation to the spleen involved the collection of data in a form which would allow the analysis and comparison of ten factors. Four of these referred to the marrow: erythrogenesis, leukogenesis, vascularity, and density of marrow cells. Four referred to the blood stream: the hemoglobin content, the erythrocyte count, the leukocyte count, and a differential study of the blood cells. Two referred to the laboratory animal in a general way; its weight at regular intervals and parallel notes on its general condition, such as the healing of the operative wounds and the absence or presence of any influence that might affect the marrow even in a minor way.

All data were collected simultaneously just before taking each specimen of marrow. This parallelism of observations not only justified comparison of data, but also contributed to a much more comprehensive knowledge of what occurs after removal of the spleen than could be secured by studying the marrow alone.

Five series of experiments were carried through: Series 1, 2, 3, and 4 failed to accomplish exact experimental control. My report is based largely on the findings by the new method of experimental control used in the experiments in Series 5. Brief reference will be made to the first four series because they bring out certain points which are important when studied in conjunction with the findings in Series 5.

Series 1.—The marrows from the tibias of twenty-five rabbits, thirteen splenectomized and twelve nonsplenectomized, for periods up to fourteen months after splenectomy, were studied. The marrows of the splenectomized rabbits were controlled by the marrows of the nonsplenectomized rabbits.

Series 2.—The marrows from the femurs (central third) of fourteen dogs, eight splenectomized and six nonsplenectomized, for a period of more than one year after splenectomy, were studied. In this series also the splenectomized animals' marrows were controlled by the nonsplenectomized animals' marrows.

Series 3.—The marrows from the femurs of two goats, of the same age, one splenectomized when three weeks old, and one nonsplenectomized, for a period of fifteen months after splenectomy, were studied. In this series also the nonsplenectomized goat was a control for the splenectomized goat.

Series 4.—The marrows from the central third of the left femur of each of six dogs, three splenectomized and three nonsplenectomized, taken at the end of the experiment, were compared with the marrows taken as controls before splenectomy from the center of the right femur from each of the same dogs.

Series 5, A.—The marrows from the ribs, taken at frequent intervals from fourteen dogs, eight splenectomized and six nonsplenectomized, operated on under ether anesthesia and by sterile technic, were studied.

Series 5, B.—The marrows from the ribs of four dogs, two splenectomized and two nonsplenectomized, were studied in the same manner as in Series 5, A except that cocain anesthesia was used instead of ether.

METHOD OF OBTAINING RIB MARROW SPECIMENS

A piece of rib 4 cm. long was removed from a point midway between the spine and sternum. This specimen, removed before splenectomy, from a healthy and apparently normal dog, constituted the control for subsequent pieces of rib removed from the same animal at regular intervals after splenectomy. The six dogs in Series 5, A not splenectomized and used as additional control had exactly the same treatment, including the rib resections and abdominal incisions, except that after the spleen was delivered outside the abdomen and traction and trauma were exerted, such as were estimated to equal those of splenectomy, the spleen was returned to the abdomen and the wound closed. Thus each specimen of marrow was controlled by a specimen from the same animal before the splenectomy, as well as by the similar series of rib resections from nonsplenectomized animals. Test examination of many specimens from similar parts of the ribs has proved that the marrow from the same relative position of several ribs from the same animal is very similar in cell character and activity.

By this method as many as nine specimens of rib marrow from a single animal were secured at intervals of from two weeks to several months during a total period of fifty-four weeks' observation. Thus in Dog D32 the first rib marrow specimen, removed before splenectomy, was the control. The second specimen was removed two weeks after splenectomy, the third five weeks after, the fourth nine weeks, the fifth seventeen weeks, the sixth twenty-nine weeks, the seventh forty-one weeks, and the eighth fifty-four weeks. In connection with this experiment a nonsplenectomized dog was put through exactly the same routine rib resections with the same intervals between resections, as an additional control.

Before each operation the blood was examined for the number of leukocytes and erythrocytes, and the hemoglobin estimation. Similarly before each operation a record was made of the animal's general condition, the healing of former wounds, and the weight. In three experiments of Series 5, A blood smears were also made at frequent intervals to check the types of blood cells and compare them with the cells seen in the marrow of the same animals. At the end of the experiment the animals were etherized and necropsy was performed in order to insure that they were not affected by disease or any factor except absence of the spleen.

Great care was taken to rule out animals in which a complication might introduce an additional factor affecting the marrow. Of a series of thirty-nine rabbits, fourteen were excluded from consideration owing to wound infection, "snuffles," pregnancy, and so forth. Empyema, pregnancy, and suppurative cystitis of unknown cause required the rejection of three dogs. In a few cases the experiments were continued in animals in which a very slight and superficial stitch infection occurred. In these cases the presence of such a factor was noted and clearly marked on the charts so that due significance might be attributed to the condition. These wounds healed readily, however, and if they were of significant influence on the marrow function it could be for a brief period only, and probably at the most no more than one marrow specimen was affected.

The animals were kept on a uniform diet throughout the experiment, except two animals, who became so thin and anemic at one period shortly after splenectomy that for a short time they were given meat and milk in addition to the regular diet.

None of the animals finally retained as satisfactory for marrow study died because of sickness. Every animal when etherized, except Dog D376, appeared to be as healthy as when the experiment was begun, June, 1919. This animal appeared perfectly healthy up to May 12, 1920, when he died suddenly. Necropsy showed acute meningitis. Five marrow specimens, the last of which was taken April 8, were retained because the animal was healthy for a month after these specimens were taken. The final marrow specimen was not included in the report because it was probably affected by the terminal febrile infection.

At necropsy not only were numerous specimens of femur and rib marrow taken, but also lymph nodes and hemolymph nodes were preserved for study. A general search was made for any pathologic condition, special attention being given to the chest. In no case was there any sign of empyema or even adhesions from pleurisy.

A separate series of animals was studied, using cocain anesthesia, in order to investigate whether the anesthetic is a complicating factor.

PREPARATION OF RIB MARROW SPECIMENS FOR MICROSCOPIC STUDY

A piece of rib approximately 4 cm. long is removed midway between the spine and the sternum. It is advisable to remove a subsequent specimen of rib marrow from the opposite side of the chest, or at least one or two ribs distant from the previous site or rib resection, in order to insure the absence of local inflammatory reaction in the region from which a new marrow specimen is to be taken.

The rib marrow specimen is held firmly against a block of wood and is cut into five pieces with a sharp, fine saw, with care not to squeeze out the marrow or injure it, except at the site of actual cutting. The pieces from each end of the specimen are thrown away because at these points the marrow cells are crushed out of their normal relationship. Three pieces of rib approximately 1 cm. long are thus secured for fixation and section.

Several methods were tried before satisfactory rib marrow sections were prepared by the following steps:

Specimen.—A small specimen is placed in Zenker's solution (without glacial acetic acid) for twenty-four hours.

The specimen is washed in running water for twenty-four hours.

The specimen is placed in 5 per cent nitric acid and changed daily until the block is soft enough to be cut. This requires for from three to seven days. If the rib has a very thick hard bone cortex a 10 per cent solution of nitric acid is necessary.

The specimen is washed in running water for twenty-four hours. An attempt to facilitate the process of washing out the acid by use of sodium bicarbonate solution results invariably in "hazy" or "muddy" sections. Ordinary tap water is found to give the most satisfactory results.

The specimen is placed consecutively in:

80 per cent alcohol for twenty-four hours.
95 per cent alcohol for twelve hours.
Absolute alcohol for three hours.
Equal parts of absolute alcohol and cedar oil for one hour.
Cedar oil for one hour.
Chloroform (two changes) for one hour.
Equal parts of chloroform and paraffin for one hour.
Paraffin (two changes) for two hours.

The specimen is then embedded.

Sections.—The section is made 7 microns thick.

For staining, the section is run through toluene and graded alcohol to water (about two minutes in each solution) as follows:

Toluene (two changes).
Absolute alcohol (two changes).
95 per cent alcohol.
70 per cent alcohol.
50 per cent alcohol.
Distilled water.

The section is left about five minutes in 5 per cent eosin. The tendency is to overstain with eosin.

The section is washed through two waters.

The section is stained with polychrome methylene-blue (Goodpasture's) for about two minutes.

The section is immersed in 95 per cent alcohol (two changes) for about two minutes each. It is then examined under the microscope; if it is too blue it is again washed in 95 per cent alcohol; if it is not blue enough it is returned to water and restained.

The section is washed with absolute alcohol for about two minutes, and xylene or toluene for about two minutes.

The section is mounted with Canada balsam and is then ready for the histologic study.

METHOD OF RECORDING OBSERVATIONS ON BONE MARROW

Observations involving a close microscopic study of the marrow with oil immersion lens were essentially processes of comparison; pathologic marrow was compared with normal, hyperactive marrow with a normal or sluggish marrow, very vascular marrow with relatively slightly vascular marrow, and a marked density of marrow cells was numerically compared with a marrow containing a few scattered marrow cells amid masses of fat cells.

In order to compare and record marrow findings the following system of grading activity, vascularity, marrow cell density, and so forth, was adopted.

Erythrogenesis.—Grade 1 is the most sluggish erythrogenesis observed. It consists of a field in which most of the cells are primitive cells, myeloblasts, myelocytes, and fat cells with a few scattered normoblasts and megaloblasts as evidence of erythrogenesis. Grade 4, on the contrary, indicates the most active type of erythrogenesis observed in any rib marrow. Grades 2 and 3 are intermediate between Grade 1 and Grade 4.

By much practice it finally proved possible to grade specimens of marrow so that the gradings of the same specimen varied no more than one-half of one grade, even though the examinations were made weeks apart, so that each subsequent grading was unprejudiced by recollection of the previous grading.

Leukogenesis.—Gradings of leukogenesis are made in exactly the same manner as of erythrogenesis.

Vascularity.—Grade 1 is a marrow with only a few small capillaries moderately filled with erythrocytes. Grade 4 is a marrow containing numerous capillaries and sinuses congested with erythrocytes. Grades 2 and 3 are intermediate between Grade 1 and Grade 4.

Cell density.—Grade 1 of marrow cell density represents a rib marrow with small islands of marrow cells with considerable fat; the bone cortex and bony trabeculæ and septums which divide the marrow compartments in the rib are quite thick. Grade 4 represents a rib marrow containing large islands of dense marrow cells with little or no fat; often these large islands of marrow cells become confluent and the bony septums become fewer and thinner. The bone cortex also undergoes a change and is thinned out and honeycombed by numerous new small islands of marrow cells. Grades 2 and 3 constitute intermediate grades between Grade 1 and Grade 4.

General activity.—General activity of marrow is estimated by computing the mean of four factors: erythrogenesis, leukogenesis, vascularity of the marrow, and density of marrow cells. Thus, for example if in a given specimen of marrow erythrogenesis is estimated as Grade 3; leukogenesis, Grade 2; vascularity, Grade 2, and density of marrow cells, Grade 3, the general activity, by averaging the four grades, would be computed to be Grade 2.5.

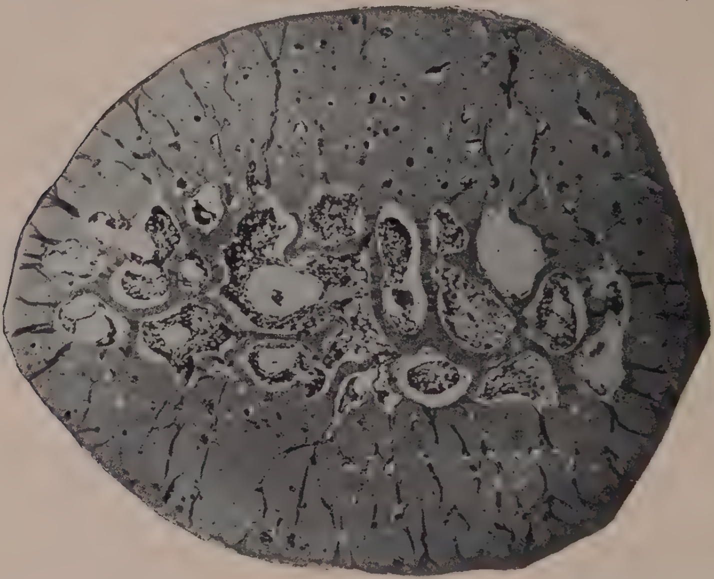

FIG. 151 (D208).—Specimen of sluggish marrow, characterized by the large amount of fat, the thick bone cortex, the thick bony septums, and the small islands of marrow cells which honeycomb the bone cortex. (× 18.)

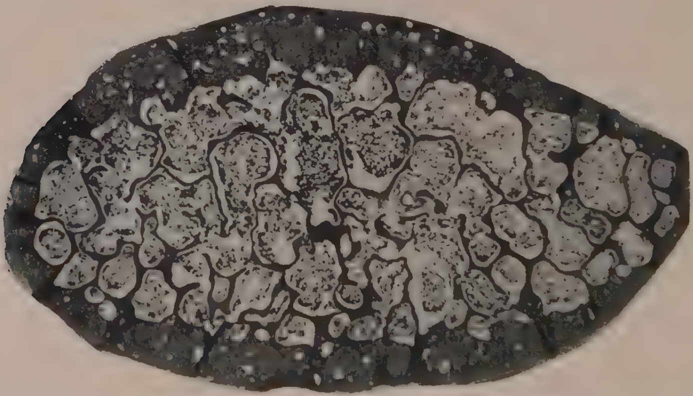

FIG. 152 (D239).—Specimen of moderately active rib marrow, characterized by the large amount of fat (white), few marrow cells, the thin bone cortex, and thin bony septums which separate the islands of marrow cells. (×18.)

This is a purely arbitrary method of recording data, but if the observations are all made by one investigator who carefully maintains the same grading throughout the study, the figures secured furnish a convenient and accurate basis for comparison of different marrow specimens. Such a system of records also permits plotting curves representing marrow activity, and so forth, and it thus becomes possible to present the results of the experiments in a graphic form that is definite and readily comprehended.

Nine curves were made for each of the ten splenectomized and eight nonsplenectomized dogs (Series 5, A and 5, B). The nine curves plotted for each animal experiment form three groups: Group 1 consists of five curves: erythrogenesis, leukogenesis, vascularity, cell density, and general activity. This group of curves, therefore, indicates the condition of the marrow. Group 2 consists of three curves: the white cell count, the red cell count, and the hemoglobin estimation. These show the parallel blood findings. Group 3 consists of one curve and notes which give the animal's weight, general health and condition

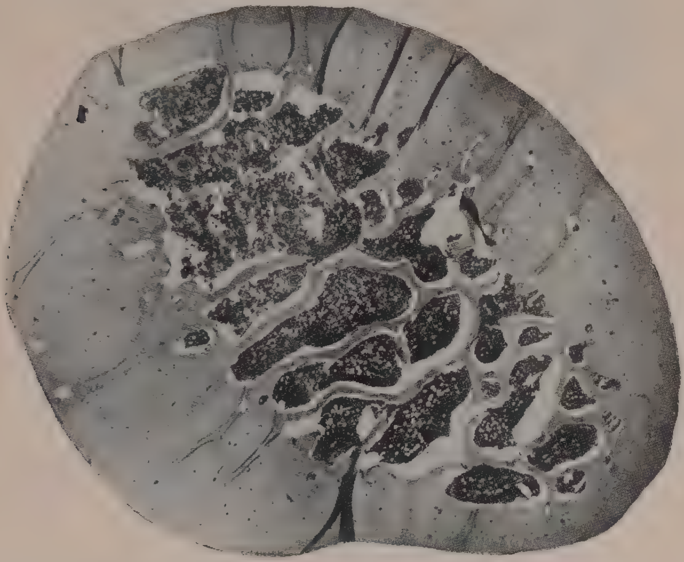

Fig. 153 (D232).—Specimen of very active rib marrow, characterized by few fat cells, many normoblasts, and megaloblasts whose deeply staining nuclei give a dark color to the photomicrograph, and large islands of marrow cells which are confluent in places. (×18.)

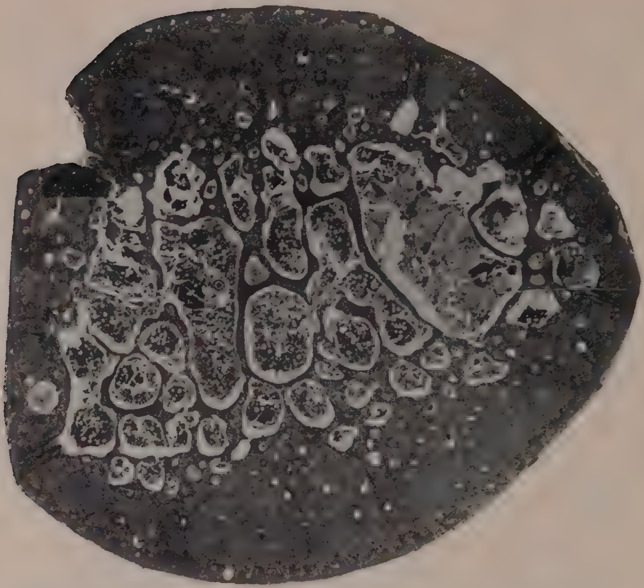

Fig. 154 (D230).—Specimen of moderately active rib marrow, showing the process of formation of new marrow cells in the bone cortex. (×18.)

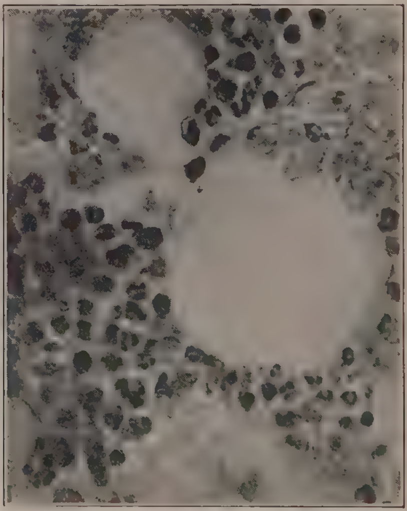

Fig. 155 (D230).—Specimen of rib marrow of a dog taken two weeks after splenectomy, characterized by the presence in the marrow of myelocytes, metamyelocytes, mature polymorphonuclears, and the primitive undifferentiated mother cells. (×600.)

of his wound, and the findings at necropsy, all being made to parallel the marrow and blood observations.

A STUDY OF THE MARROW OF VARIOUS ANIMALS

It has been customary to use one animal as a control for another animal in a study of the marrow. For instance, one of two dogs is splenectomized. At the end of a certain period, six months, for example, the two animals are killed by ether, and their marrows, usually the central third of the femur marrow, are compared. If the marrow of the splenectomized animal is much more active than that of the nonsplenectomized animal, it is assumed that splenectomy causes an increase in marrow activity.

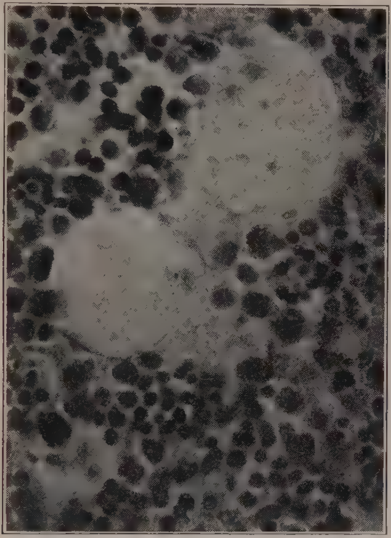

FIG. 156 (G82).—Specimen of femur marrow of a splenectomized goat taken fifteen months after splenectomy, characterized by numerous esoinophilic myelocytes and active erythrogenic groups. (×600.)

In my first three series of experiments I undertook to use one animal to control another, but certain observations led me to suspect that the marrows of apparently healthy and normal animals differ markedly. Therefore, I determined to make a special study of the question.

Comparisons were made of gross and microscopic specimens of the marrows from the center of the femurs of ten healthy dogs, all approximately of the same age and all adapted to laboratory conditions, on a standard diet. The marrows of five dogs were graded 1 to 1.5, of three 2 to 2.5, and of two 3 to 3.5. Thus, in a series of ten healthy normal dogs picked at random, there was a very marked difference in the

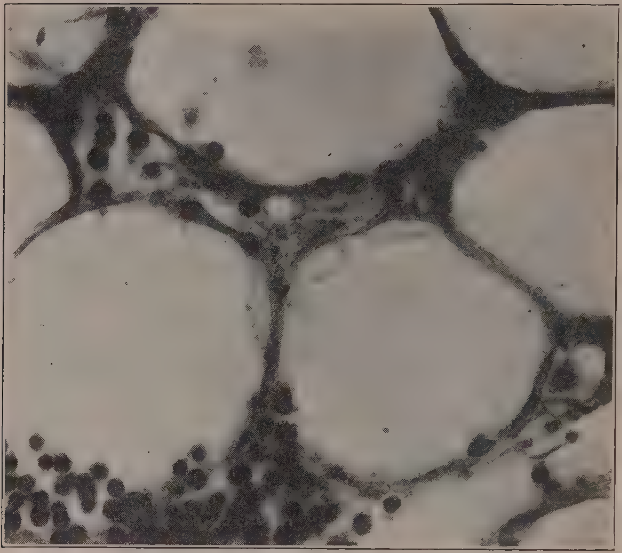

Fig. 157 (G79).—Specimen of femur marrow of a nonsplenectomized goat, characterized by a framework of marrow with large fat spaces and a few groups of erythrogenic marrow cells. (×600.)

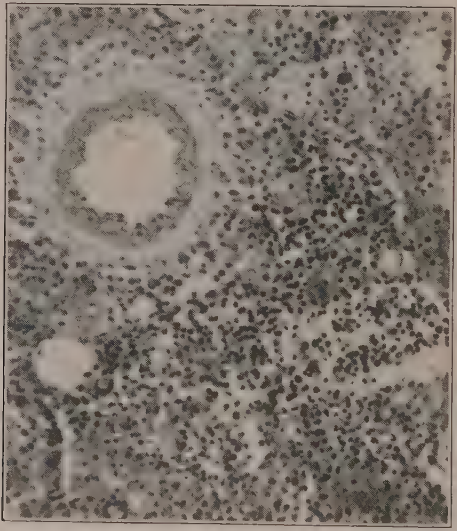

Fig. 158 (D32).—Specimen of rib marrow of a dog taken nine weeks after splenectomy, characterized by large spaces which are relatively inactive and others which are very active. (×200.)

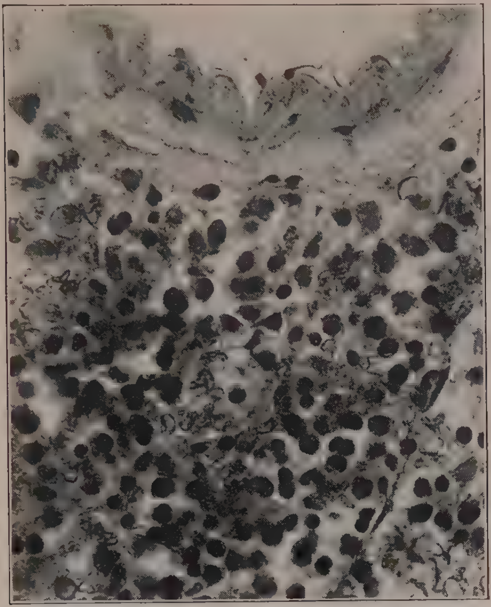

FIG. 159 (D32).—Specimen shown in Figure 158 at a higher magnification, showing the mixed erythrogenesis and leukogenesis. (×600.)

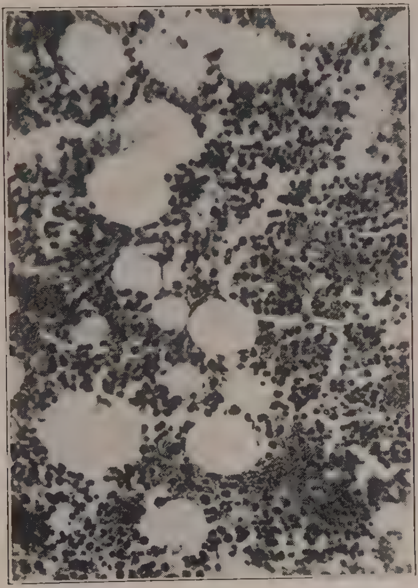

FIG. 160 (D32).—Specimen of rib marrow of a dog taken seventeen weeks after splentectomy, characterized by numerous normoblasts indicating active erythrogenesis. (×200.)

marrows. It is apparent that one dog's marrow cannot be used as a control for that of another in laboratory experiments, and when it is considered that the dogs used for experimental purposes are of the most varied mongrel breeds, it is not surprising that their marrows also vary in character.

A similar study was made of the marrows of the tibias of twelve rabbits. The erythrogenic activity of the marrows of two rabbits was graded 1, of six 2, and of four 2 to 3. The leukogenic activity of the marrows of seven rabbits was graded 1, of the marrow of one rabbit 1 to 2, of the marrows of two rabbits 2 to 3, and of the marrow of one rabbit 3.

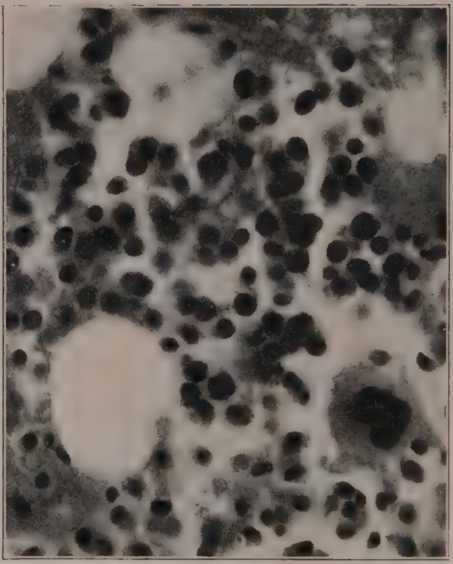

FIG. 161 (D32).—Specimen shown in Figure 160 at a higher magnification, showing the maximal degree of activity after splenectomy. (×600.)

These findings show how varied are the marrows of individual rabbits, even though many of these were from the same litter and grew up under identical environmental conditions, and that it is unsafe to use one rabbit to control another in an experimental study of the marrow.

Specimens of marrow from the ribs midway between the spine and sternum were taken from fourteen healthy normal dogs. The erythrogenic activity of the rib marrows of nine dogs was graded 1, of two 1.5, and of three 2. The leukogenic activity of the rib marrows of seven dogs was graded 1, of two 1.5, of three 2, and of two 2.5. Because these experiments showed the fallacy of controlling experiments on the marrow of one animal with the marrow of another, I devised a new method of control as used in Series 5 of the experiments. The essential feature of this method is the removal of a specimen of rib marrow before splenectomy for a control of successive specimens taken from the same animal after splenectomy.

HISTOLOGY OF THE BONE MARROW

In all main respects I agree with the admirable description of marrow cell groups by Pearce and Krumbhaar, whose groupings were a modification of those previously made by Bunting. Valuable descriptions of the morphology of the cells in the marrow were found in Gruner's "The biology of the blood cells."

Marrow cell groups are usually mixed, erythrogenic and leukogenic. Very rarely a purely erythrogenic or purely leukogenic group is found, but commonly in groups of marrow cells erythrogenesis or leukogenesis predominates so largely as to justify the description of the group as essentially one or the other. After a close study of the function of the marrow of the femur and rib of the same animal I have been convinced that leukogenesis is more active in the rib.

Because the rib marrow quickly shows changes in activity and reveals small degrees of change, it is well adapted for study. The central third of the femur marrow, on the other hand, is tardy in showing changes in activity, and only after quite marked changes in the marrow function elsewhere is there a perceptible modification of the marrow of the central third of the femur. For these reasons the rib marrow is a better index of change than the femur marrow.

My observations on the marrow of the dog did not lead me to believe it to be a seat of active production of lymphocytes. Because Gulland and Goodall describe very active lymphogenesis in some marrows, I made a special study of this matter. Specimens of spleen, lymph glands, hemolymph glands, and ribs were taken from the same animal. Direct comparison of similarly stained specimens was made between known lymphocytes in the spleen and glands with lymphocyte-like cells in the marrow; the micrometer was frequently used to compare exactly the relative sizes. By such a direct comparison of cells in specimens arranged under adjacent microscopes, I was convinced that a few lymphocytes occur in the marrow and are, apparently, generated there. A significant degree of lymphogenesis was observed, however, in isolated marrow specimens of two animals only. It appears that lymphogenesis can occur in the marrow and that a slight degree may be common, but a noticeable active lymphogenesis is rare.

One very interesting phase of the histology of the marrow is the method by which the rib marrow increases its capacity. This increase is accomplished by several changes which may operate separately or all together. The earliest and most common method is for marrow cells to replace the fat cells, which are abundant in a sluggish marrow. If there is a continued demand for hyperplasia and hyperactivity of the rib marrow beyond that which can be met by simple replacement of fat cells by marrow cells, an enlargement of the rib marrow cavity is produced by a thinning of the bone cortex and the bony septums which divide the rib cavity into compartments. This process consists of not only a general thinning of the bone cortex of the rib, but also a "honeycombing" by small islands of marrow cells which become larger as hyperplasia increases. When specimens were prepared from rib resections soon after splenectomy it was necessary to use a sharp saw and cut through quite a hard thick bone cortex, but as hyperplasia increased in the rib marrow the rib specimens became changed so that at times it was even possible to cut the rib sections with a knife instead of a saw, and even macroscopically the thinning of the bone was evident.

As the rib marrow space was thus increased in size there were simultaneous changes in the character of the marrow cells therein. In a sluggish marrow most of the cells are primitive cells, myeloblasts, and myelocytes; normoblasts, megaloblasts, and metamyelocytes are few. But as the marrow becomes active there is a greater preponderance of these intermediate forms. Large numbers of megaloblasts and normoblasts mean an active erythrogenesis. Numerous metamyelocytes fringed by more mature leukocytes are likewise interpreted as a sign of active leukogenesis. When a series of eight or nine marrow specimens, taken at regular intervals during a year or more after splenectomy, is studied under the microscope so as to trace the marrow changes step by step, it is of fascinating interest to observe how hyperplasia and hyperactivity are accomplished at the same time (Figs. 151–161).

DETAILED SUMMARY OF FINDINGS

A summary of the observations regarding the influence of splenectomy on the bone marrow is essentially an analysis of the charts (Figs. 161–169) on which the data have been concentrated. One of the series of protocols has been appended as a typical illustration of the experimental procedure and the manner of recording data.

Changes in the erythrogenic function of the marrow after removal of the spleen of a normal animal.—If the findings relating to the rib marrow changes in the six splenectomized animals of Series 5, A (operated on under ether anesthesia) are correlated, the average erythrogenic reaction may be summarized (Table 1 and Fig. 162).

TABLE 1

Erythrogenesis in the Marrow of Six Dogs After Splenectomy

	D32.	D230.	C981.	D207.	D208.	D979.	Average.
	Weeks.	Weeks.	Weeks.	Weeks.	Weeks.	Weeks.	Weeks.
Time before an observable increase in erythrogenesis...............	5 to 9	2 to 4	2 to 4	5 to 9	8 to 12	0 to 2	About 4
Time when maximal erythrogenesis is reached.....................	17	8	8	13	12	2	8 to 12
Duration of maximal erythrogenesis	6	20 to 25	8 to 12	6 to 8	12 to 20	15 to 20	12
Time when erythrogenesis has decreased to fairly constant degree (somewhat above normal).......	30	*	20	33	44	†	28 or more†

* Erythrogenesis still very active on completion of the experiment at the thirty-seventh week.
† Erythrogenesis still very active on completion of the experiment at the forty-fourth week.

1. There is, on the average, a latent period of four weeks before an increase in erythrogenic activity is observable.

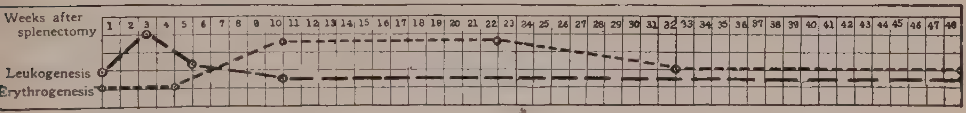

Fig. 162.—Average reaction of the rib marrow after splenectomy.

2. Increased erythrogenesis, first observable about four weeks atfer splenectomy, attains its maximal degree of activity after from eight to twelve weeks.

3. Maximal erythrogenic activity attained about twelve weeks after splenectomy persists practically unabated for about twelve weeks.

4. Thereafter the production of red blood cells decreases gradually until a period varying from twenty-eight weeks to one year or more after splenectomy, when it reaches a more or less constant degree of activity, which, however, is still considerably above normal, that is,

above the degree of erythrogenesis observed in the marrow of the same animal in a specimen removed before splenectomy.

5. Increased erythrogenesis is observable in the marrow for a period of four weeks or more, before any reduction in the anemia following splenectomy is evident. This is graphically illustrated by the respective curves on the charts (Figs. 163, 164, and 167), the erythrogenesis curve rising some time in advance of the hemoglobin and erythrocyte curves.

6. A further comparison of erythrogenesis with other factors, which were studied at the same time, shows certain very interesting parallelisms. On the one hand, erythrogenesis, marrow vascularity, and marrow cell density simultaneously increase, and on the other hand, the hemoglobin, the red cell count, and the animals' weight form a group with curves running remarkably parallel courses, first downward, during the development of the anemia, and then upward until they reach or exceed a normal level.

Changes in the leukogenic function of the marrow after removal of the spleen of a normal animal.—Three of the six animals whose spleens were removed under ether anesthesia showed a spectacular increase in marrow leukogenesis. This reaction, occurring in only 50 per cent of the animals operated on under ether anesthesia, occurred immediately, and lasted only for from two to five weeks after splenectomy.

If, in conjunction with the foregoing observations of the rib marrow, the leukogenic reaction in the tibia marrow of twelve splenectomized rabbits, studied after the effect of ether anesthesia had presumably subsided, is considered, I am inclined to believe that splenectomy itself is a factor in the cause of increased marrow leukogenesis. The ether used as an anesthetic for splenectomy seems to be at least a contributing factor in causing the leukogenic reaction. This question of the real cause of the spectacular increase in leukogenic activity after splenectomy will be considered more fully in the discussion which follows.

There is an exact parallelism between the high leukogenesis in the marrow and the concurrent high leukocytosis in the blood stream (Fig. 163).

Changes in the tibia marrow of rabbits following splenectomy.—The findings in the study of rabbit marrow were charted and retained in this report to illustrate two points: (1) the very marked differences in the marrow of apparently healthy animals so that comparisons

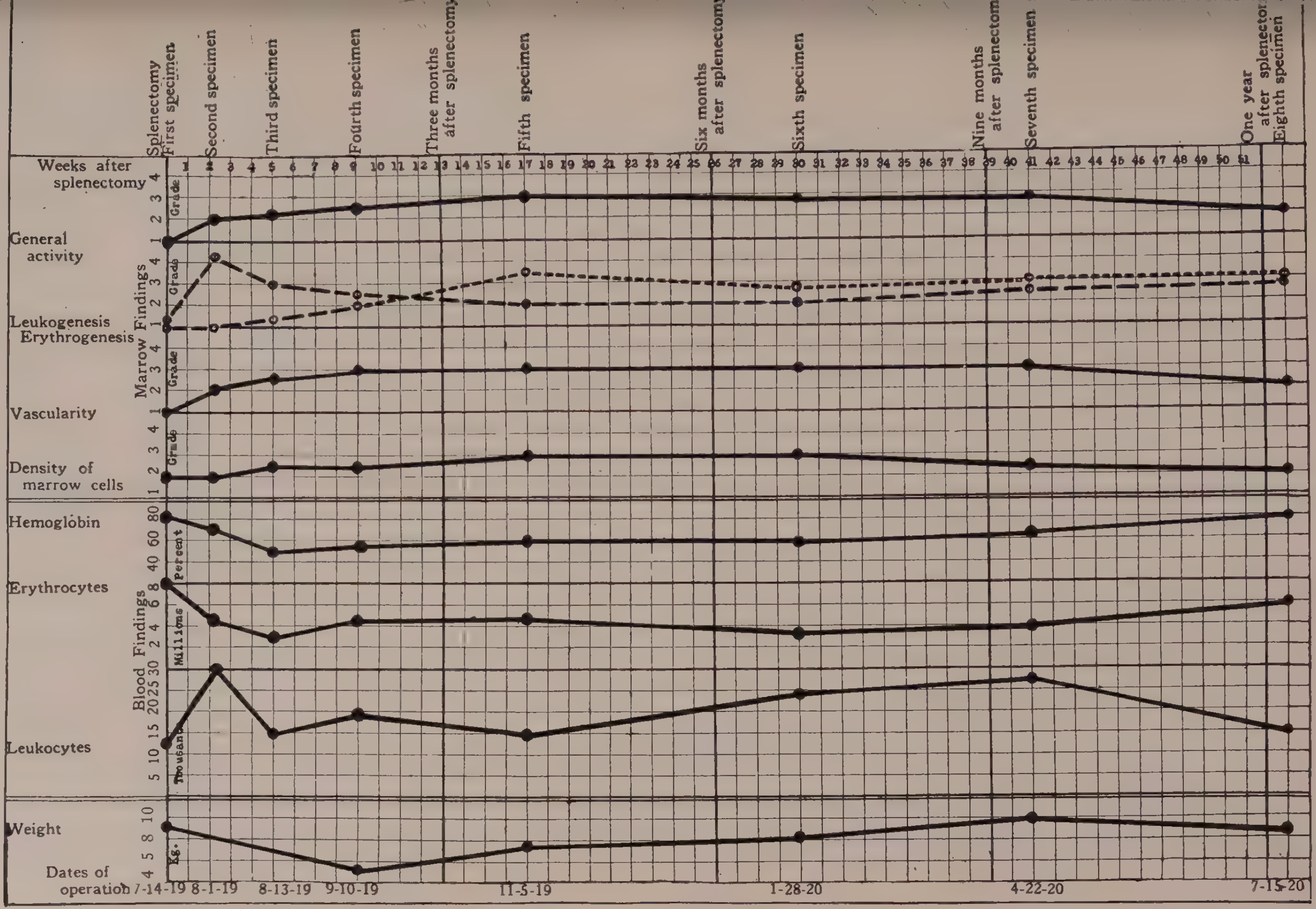

FIG. 163 (D32).—Changes in the marrow, blood, and general condition after splenectomy under ether anesthesia. Eight rib marrow specimens were removed under ether during one year. The findings are similar to those in two other experiments (D230 and D979). July 14, 1919, animal healthy; August 1 and August 13, very severe postsplenectomy anemia; September 10, thin and listless, wounds clean; November 5, better condition, still thin, wounds clean; January 28, 1920, thin and rather weak, wounds clean, gradual recovery from anemia; April 22, again in good condition, wounds clean; July 15, healthy, good weight when killed. Necropsy revealed no pathologic condition.

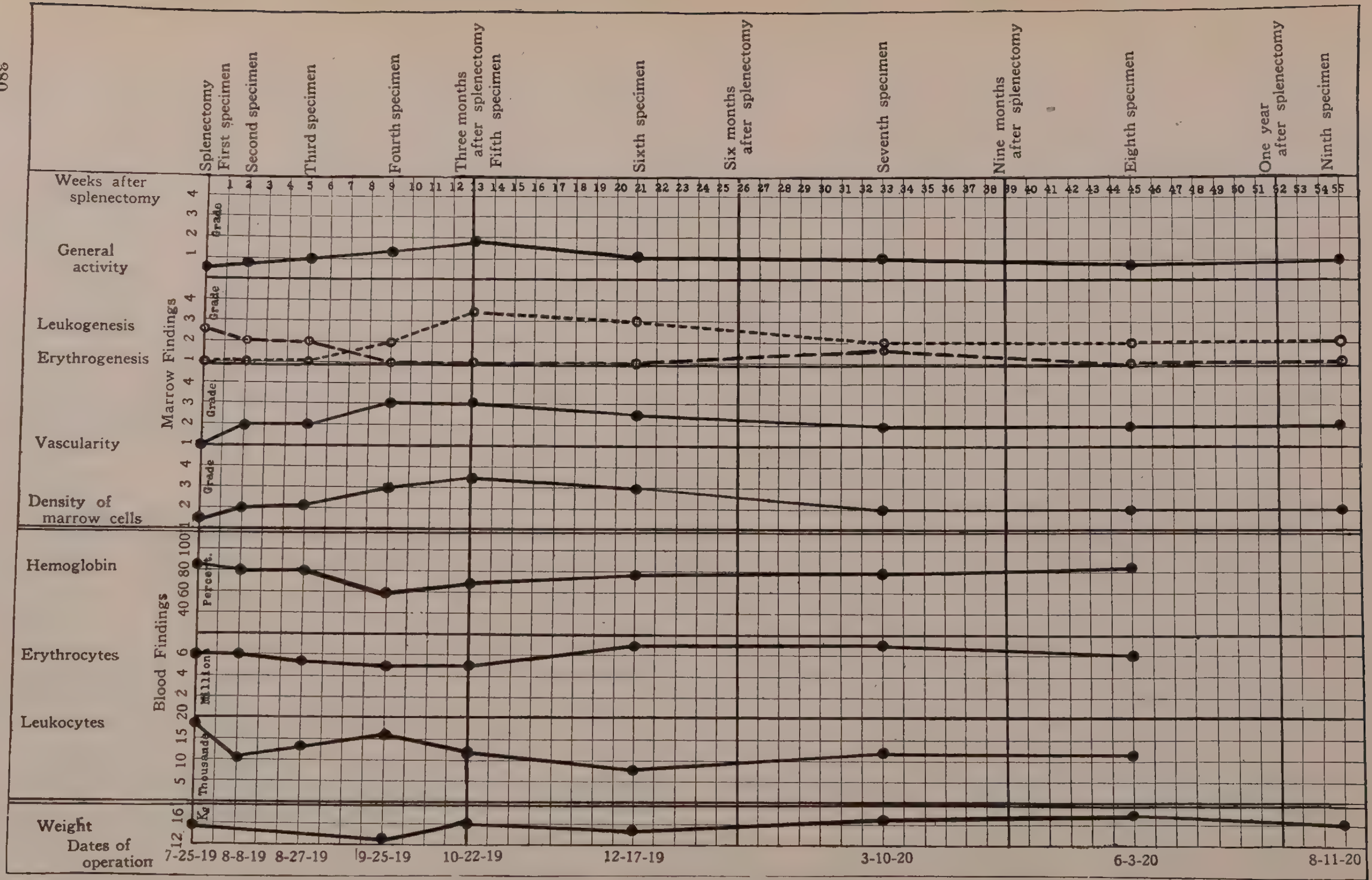

FIG. 164 (D207).—Changes in the marrow, blood, and general condition after splenectomy under ether anesthesia. Nine rib marrow specimens were removed under ether during one year and seventeen days. The findings are similar to those in two other experiments (D208 and D981). July 25, August 8, and August 27, 1919, animal healthy, had "dog fight" night before operation, leg badly bitten; September 25, good condition, wounds clean; October 22, fat and vigorous, wounds clean; December 17, fat and vigorous, wounds clean; March 10, 1920, fat and vigorous, wounds clean; June 3,

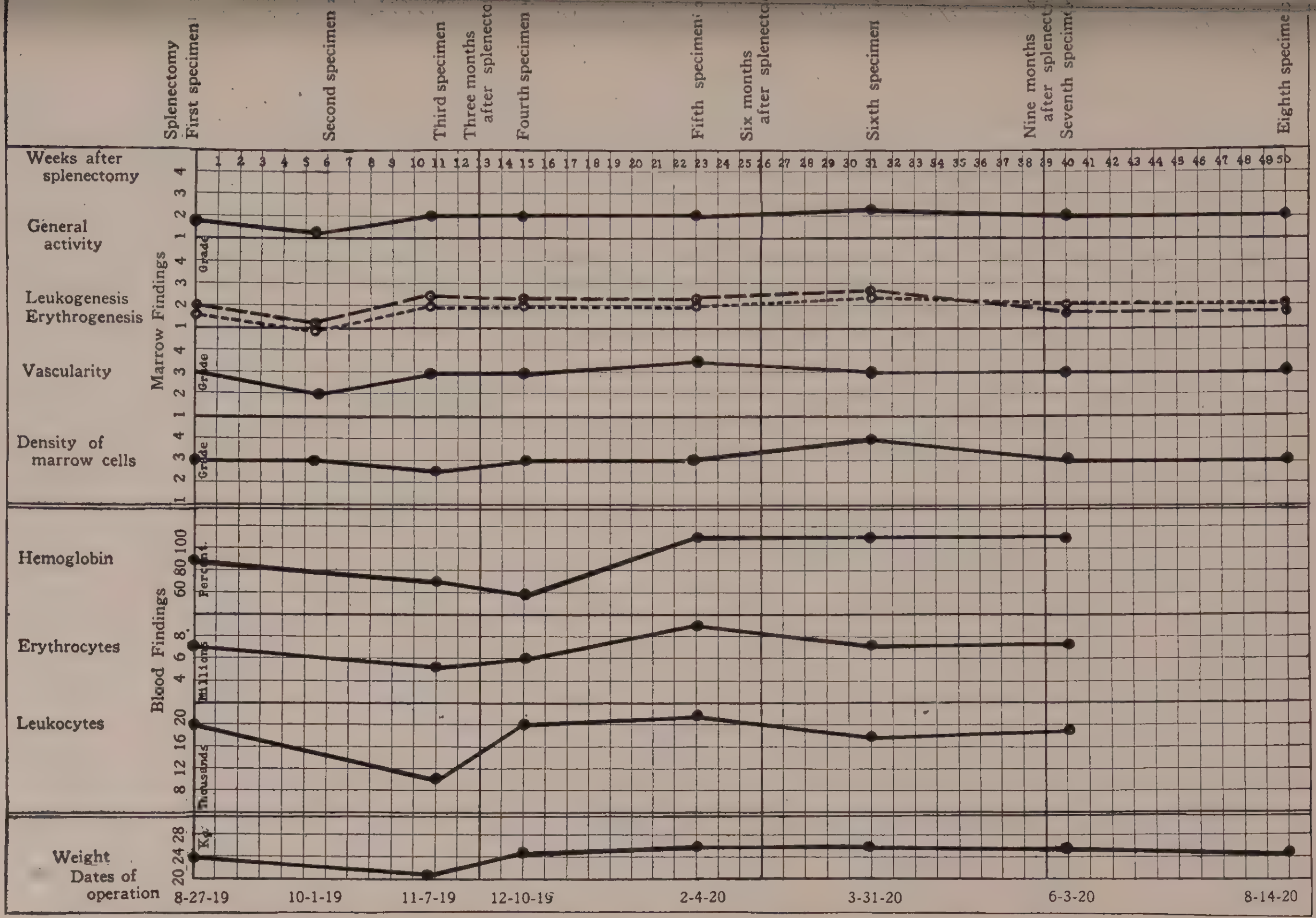

FIG. 165 (D239).—Changes in the marrow, blood, and general condition in a nonsplenectomized animal. Eight rib marrow specimens were removed under ether during fifty weeks. August 27, 1919, condition of animal good; October 1, leg fractured; November 7, thin, wounds clean, healed; December 10, healthy but thin, special diet (milk and meat); February, 4, 1920, fat, wounds clean, healthy, fracture united; March 31, fat and vigorous, wounds healed, clean; June 3, fat and vigorous, wounds healed; August 14, healthy when etherized. Necropsy revealed no pathologic condition.

appear to conflict in most respects, and (2) the increased leukogenesis in the marrows of the twelve splenectomized rabbits during the first few months after splenectomy when compared with the marrows of thirteen non-splenectomized rabbits (Figs. 169 and 170).

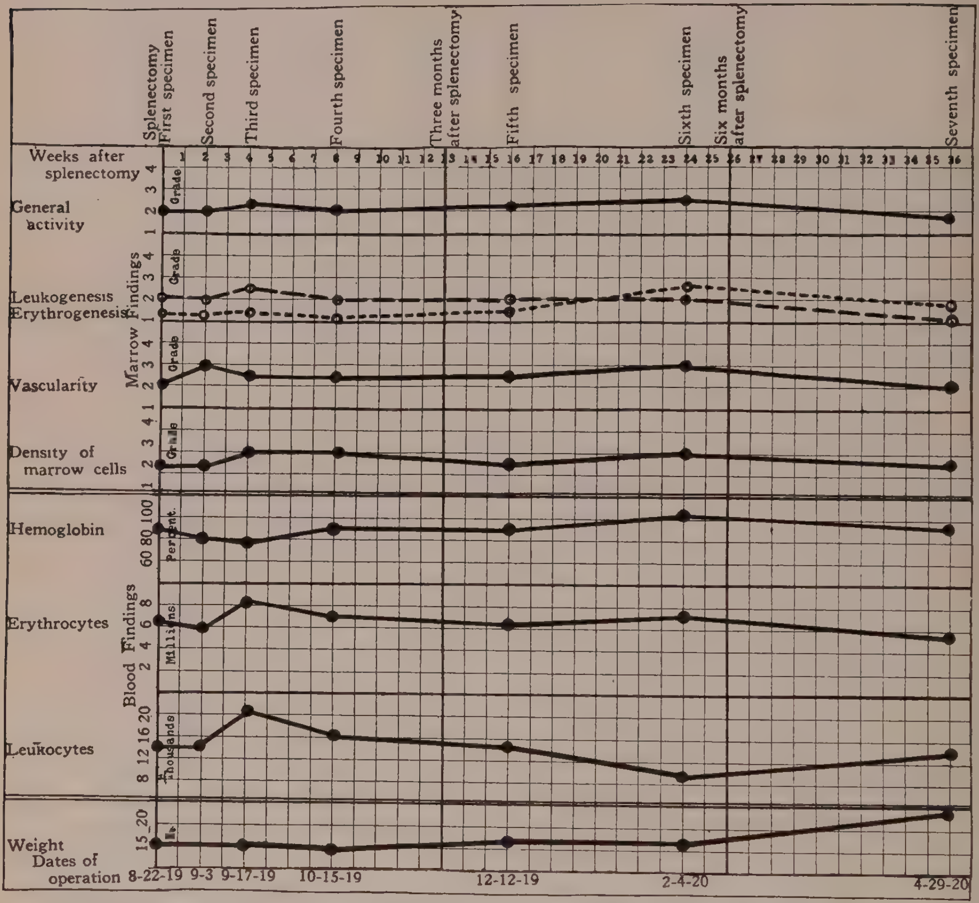

FIG. 166 (D233).—Changes in the marrow, blood, and general condition in a non-splenectomized animal. Seven rib marrow specimens were removed under ether during nine months and one femur marrow specimen was removed at the beginning of the experiment. The findings are similar to those in two other control experiments (D294 and D240). August 22 and September 3, 1919, animal healthy; September 17, wounds clean, femur fractured; October 15, healthy, wounds clean; December 12, good condition, wounds clean; February 4, 1920, healthy but slightly underweight, wounds clean; April 29, fat, healthy when killed, wounds clean. Necropsy revealed no pathologic condition.

Changes in the marrow in the control animals.—The study of the marrows of many nonsplenectomized animals at intervals of from six to fifteen months revealed the variations from time to time in the

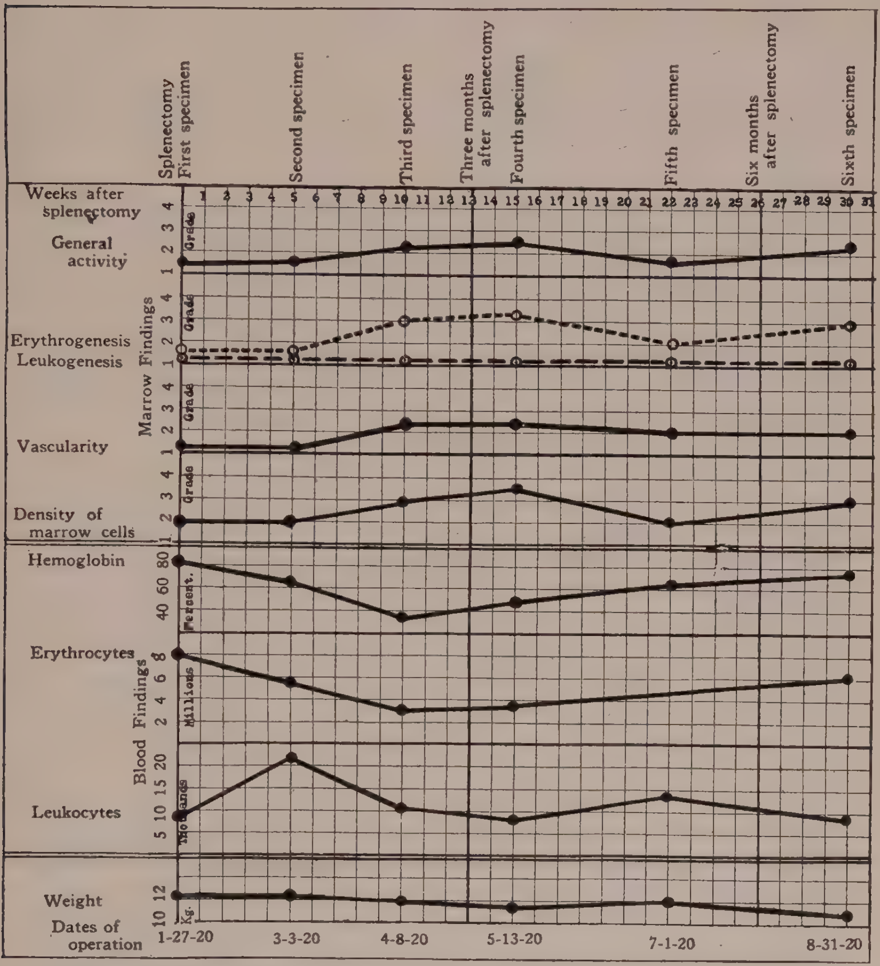

FIG. 167 (D347).—Changes in the marrow, blood, and general condition after splenectomy under cocain anesthesia. Six rib marrow specimens were removed under cocain anesthesia during thirty weeks. The findings are similar to those of one other experiment (D376). Animal healthy and in uniformly good condition throughout experiment. Necropsy revealed no pathologic condition, wound healed without infection.

marrows of normal animals. There is some fluctuation of the curves (Figs. 165, 166, and 168), which suggests that hemopoiesis is somewhat periodic, but in general the curves run as constantly level and

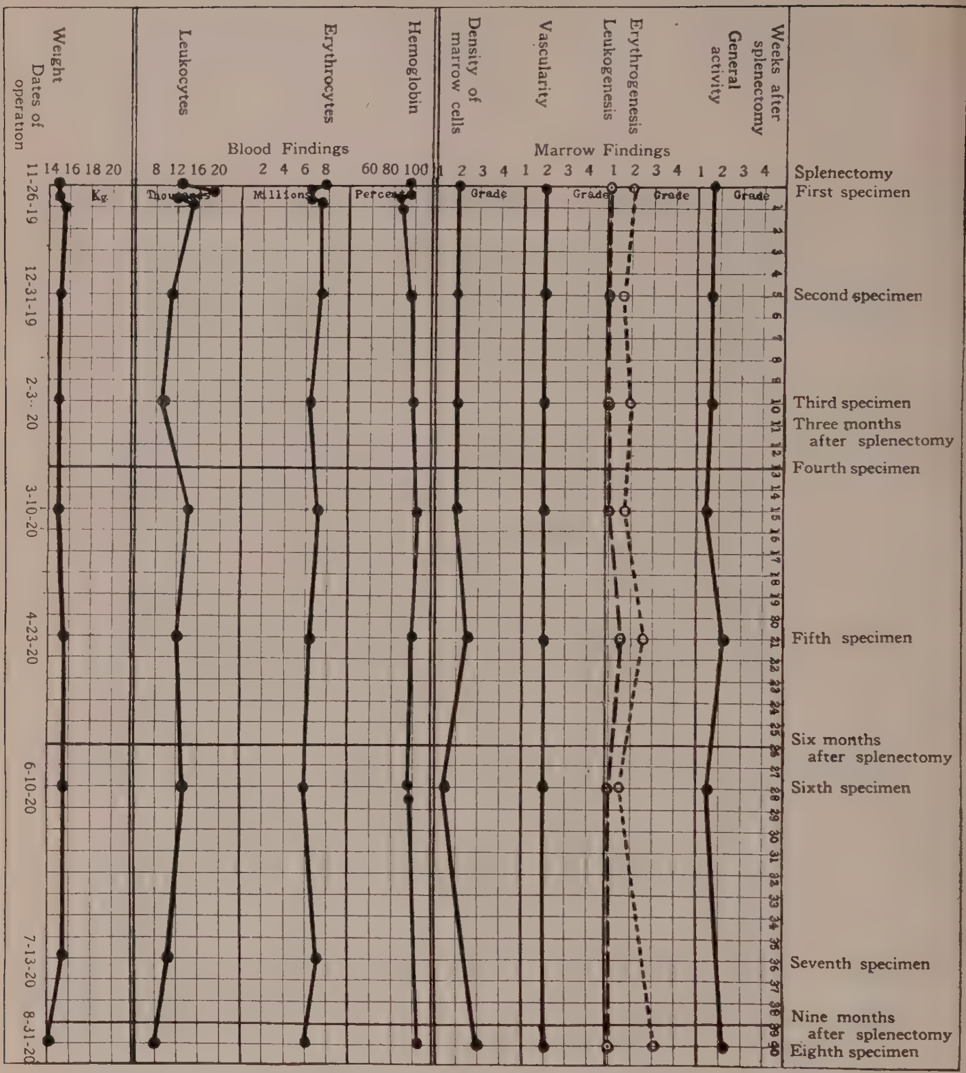

FIG. 168 (D338).—Changes in the marrow, blood, and general condition in a non-splenectomized dog. Seven rib marrow specimens were removed under cocain anesthesia during forty weeks. The findings are similar to those in one other experiment (D463). Dog in healthy condition and wounds clean throughout experiment; no pathologic condition found on examination after animal had been killed.

parallel as could be expected, considering that the observations extended through different seasons of the year and included many minor and unavoidable variations of environment.

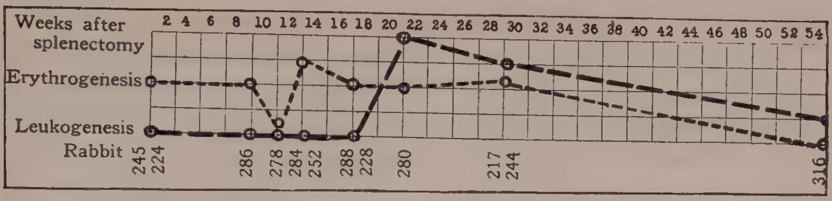

FIG. 169 (Composite chart).—Changes in the marrow of the tibias of twelve nonsplenectomized rabbits.

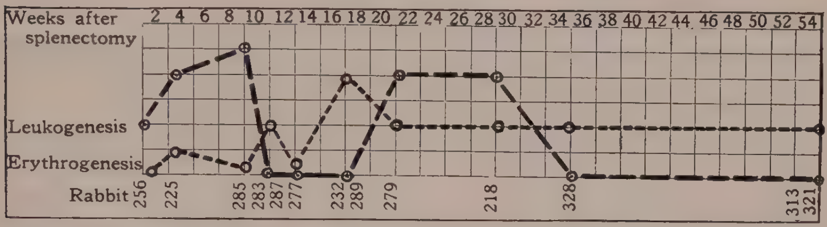

FIG. 170 (Composite chart).—Changes in the marrow of the tibias of thirteen splenectomized rabbits.

DISCUSSION

It has been clearly established that removal of the spleen of a healthy animal is followed by hyperplasia and hyperactivity of the marrow, which begins soon after splenectomy and persists for more than a year, at least. This reaction, however, may not be primarily the result of absence of the spleen. It seems more probable that the activity of the marrow is secondary to the anemia, which follows removal of the normal spleen, and is compensatory to that anemia.

It is remarkable that a definitely increased erythrogenesis in the marrow may precede, by several weeks, any signs of a reduction of the anemia following splenectomy. It is, of course, logical that signs of increased production of red cells in the marrow should precede evidence of improvement in the blood, as cause precedes effect, but the fact that a very active erythrogenesis so long precedes a reduction of the anemia indicates that whatever destructive agent becomes active after removal of the spleen, it is so potent that its effect can be compensated only by prolonged hyperactivity and hyperplasia of the marrow.

The presence of a prompt and markedly increased marrow activity after splenectomy shows that postsplenectomy anemia is due to no fault of the marrow. The presumption is, rather, that some extramedullary factor, possibly an hemolysin, is the cause. Warthin has suggested that after removal of the spleen there is excessive hemolysis in the lymph nodes which often hypertrophy. The spleen being a main site of antibody production[8], it is possible that after splenectomy the ordinary hemolytic factors act unchecked and unregulated. Whatever the cause and mechanism of postsplenectomy anemia, it is overcome by an increased activity of the marrow. It is possible that the effect of the presence of a destructive factor or the absence of a "favorable factor," normally present, gradually subsides or entirely disappears a few weeks after splenectomy so that the marrow has only to overcome a temporary disadvantage. The increased resistance of the erythrocytes after splenectomy is also a factor which probably aids in recovery from postsplenectomy anemia, especially as this increased resistance improves with the length of time after operation.

The corresponding increase in the red and white blood cells in the blood stream that accompanies an abundance of normoblasts, megaloblasts, and metamyelocytes in the marrow is strong evidence that new blood cells are being rapidly manufactured somewhere, presumably in the marrow. It occurred to me that the lymph nodes might be the site of active production of blood cells in the absence of the spleen, and I therefore removed specimens of axillary and mesenteric lymph glands from each animal. While there were, occasionally, very noticeable signs of hyperplasia in the lymph nodes and collections of normoblasts in some germ centers which were at least very suggestive of moderately active hemopoiesis, I did not observe extensive manufacture of blood cells; at least the action could not be compared with the extremely marked changes consistently observed in the marrow. The parallelism of changes in the marrow and in the blood stream is so exact that an intimate causal relationship seems certain. The objection may be made that there is no real increase of blood cells, but only a decreased destruction. Such an interpretation is not supported, however, by observations after removal of the normal spleen. All the evidence points rather to an increased destruction of red cells. Splenectomy for hemolytic jaundice, however, is a striking example of a decreased destruction of cells after removal of a presumably diseased spleen.

While I am convinced that this hypothesis is correct, that is, that increased vascularity, increased marrow cell density, and particularly the presence of numerous groups of normoblasts, megaloblasts, and metamyelocytes are evidence of increased marrow function, I must admit that such marrow changes might be explained, theoretically, on the basis of a heightened threshold of cell output, a delayed release of cells from the marrow into the blood stream, by a retarding of the rate of marrow cell development, or both these factors combined to produce an accumulation of cells in the marrow, as suggested by Ashby.

My investigations have been limited to a study of marrow changes which follow removal of the spleen of healthy and apparently perfectly normal animals. What occurs in the marrow after removal of a diseased spleen or the spleen of animals affected by such diseases as pernicious anemia, Banti's disease, kala-azar, and leukemia, may be fundamentally different. If, for example, in pernicious anemia splenectomy is followed by a long continued hyperplasia and erythrogenic hyperactivity, such as is known to follow removal of the spleen of a normal animal, we may have the explanation why some patients with pernicious anemia have shown a definite and quite lasting improvement after splenectomy, as reported recently by Giffin and Szlapka and by Giffin.

The question of the influence of ether on the marrow is puzzling. I planned to study this problem in a series of four animals, two splenectomized and two nonsplenectomized, using cocain anesthesia during splenectomy and resections of the rib. Ether does not appear to be a significant factor with regard to erythrogenesis. The splenectomized animals showed the same increase in erythrogenesis when either ether or cocain was used. The nonsplenectomized animals, equally subjected to ether and cocain, failed to show a considerable increase of erythrogenesis. Thus, splenectomy, or its resultant anemia, is clearly the precursor, and apparent cause, of increased erythrogenesis. In the study of the relation of the anesthetic to leukogenesis, however, individual variations are so marked and the leukogenic reaction so inconstant that it seems doubtful whether a series of four animals operated on under cocain anesthesia is large enough to cover individual variations. My data suggest that ether is a very important factor in the stimulation of leukogenesis. But the fact that none of the control animals showed a marked change in leukogenic activity, although they were subjected to the same degree and length of ether anesthesia as the splenectomized animals, is evidence that brief ether anesthesia alone is insufficient to affect the leukogenic function of the marrow. Mann has observed that leukocytosis usually follows prolonged ether anesthesia, that is, after three or four hours without the removal of any organ. His study, however, was limited to the blood changes. The concurrent marrow function can only be inferred from the changes seen in the blood stream.

It should be borne in mind that in my series of experiments observations of the marrow were not made earlier than two weeks after anesthesia and splenectomy. It is possible that the time of observation was too far removed from the time of stimulus to note the reaction. Further investigation is necessary to arrive at definite and clear-cut conclusions regarding the effect of an anesthetic on leukogenesis. It is certain that the erythrogenic reaction observed in the marrow is independent of the anesthetic.

It has already been suggested that the marrow reaction which follows splenectomy may be really secondary to the anemia which is known to follow removal of the normal spleen. It is possible that severe hemorrhage or repeated small hemorrhages may cause the same marrow changes as removal of the spleen. Drinker and Drinker and Kreutzman in their study of the influence of hemorrhage and infusion noted in their posthemorrhagic cases a hyperplasia of the marrow with extension into the shafts of the long bones of erythrocyte-bearing tissue and many islands showing erythrogenic activity.

Thus hyperplasia and hyperactivity of the marrow after splenectomy are probably physiologic responses to a demand for more blood cells and may have no direct relation to the absence of the spleen. Moreover, the long persistence of this marrow reaction, a persistence of hyperfunction which far exceeds the duration of postsplenectomy anemia, may be likewise an expression of the law of regeneration in excess.

SUMMARY

My conclusions regarding marrow changes after removal of the spleen are based on a series of experimental studies on twenty dogs, forty rabbits, and two goats during a period of approximately two years.

The new method of marrow study which I devised for this series of experiments consists of five essential features: (1) a rib marrow specimen removed before splenectomy is used as a control for a series of subsequent specimens removed at intervals after splenectomy; (2) series of similar rib marrow specimens from normal nonsplenectomized dogs furnish an additional control for the experiments; (3) rib marrow specimens removed at frequent intervals after splenectomy give a connected picture of marrow changes; (4) the observations on the marrow are correlated with parallel observations on the blood and on the general condition of the animal, and (5) ether anesthesia and cocain anesthesia are used in separate series of experiments in order to test the influence of the anesthetic on the marrow.

Removal of the spleen of a normal animal is followed by definite hyperplasia and hypertrophy of the marrow. The most constant and the most important change in the marrow is an increased production of red blood cells which is clearly observable, on the average, within four weeks after splenectomy and which gradually increases to the maximum about the end of the twelfth week. This maximal degree of activity persists for about twelve weeks and then gradually subsides. Increased production of the white blood cells is sometimes spectacular; it occurs almost immediately after splenectomy, but it is not only inconstant, but also temporary (Fig. 162).

The reaction of erythrogenesis in the bone marrow clearly is independent of any of the anesthetics used. The series of experiments was too small for conclusive findings with regard to the effect of the anesthetics on leukogenesis.

The marrow reaction which follows splenectomy probably is secondary and compensatory to the anemia which follows removal of the normal spleen, thus representing a physiologic response to a demand for more blood cells. It may have no direct relation to the absence of the spleen. The persistence of this marrow reaction, which far exceeds the duration of postsplenectomy anemia, may likewise be an expression of the law of regeneration in excess.

PROTOCOL*

Dog D32, a mongrel terrier in good condition, weighed 9.2 kg. July 11, 1919, the erythrocytes numbered 8,000,000, the leukocytes 13,050, and the hemoglobin was 80 per cent.

July 14, under aseptic conditions, the spleen and a piece of the rib on the right side were removed. The specimens were preserved in Zenker's solution. The spleen weighed 22 gm. Examination of the first specimen of rib marrow showed large islands of marrow cells and many erythrocytes. A few normoblasts indicated sluggish erythrogenesis. Leukogenesis was more active. There was a small central cavity well filled with marrow cells. The bone cortex was thick and honeycombed with small islands of marrow cells. The vascularity was graded 1, activity 1, erythrogenesis 1, leukogenesis 1, and density 2.

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*A complete review of the literature with a bibliography, eight charts, seven photomicrographs, three drawings in color, and thirteen protocols which appear in the thesis are herewith omitted.

July 28 the erythrocytes numbered 3,736,000, the leukocytes 31,900, and the hemoglobin was 65 per cent.

August 1 a second specimen was removed under ether anesthesia. The operation lasted twelve minutes. Examination of the specimen showed numerous normoblasts suggesting some erythrogenic activity, but leukogenesis greatly predominated. The marrow was definitely more active than that of the first specimen, the control specimen; its leukogenesis was very high. The vascularity was graded 2, activity 3 to 4, erythrogenesis 1, leukogenesis 3 to 4, and density 2.

August 12 the dog appeared to be in good condition, although thin. The blood was thin, but the wounds had healed without infection. The erythrocytes numbered 3,296,000, the leukocytes 14,700, and the hemoglobin was 35 per cent.

August 13 a third specimen was removed from the left side midway between the spine and sternum. The pleura was not injured. Examination showed large islands of active marrow cells. Leukogenesis definitely predominated over erythrogenesis. The bone cortex was still thick, but the cavity was almost solidly packed with marrow cells. The vascularity was graded 2, activity 2 to 3, erythrogenesis 1 to 2, and density 2 to 3. In general, the third specimen was about the same as the second.

September 9 the wounds were clean; the animal was very thin, weighing only 5.5 kg. The erythrocytes numbered 4,290,000, the leukocytes 20,000, and the hemoglobin was 40 per cent.

September 10 a fourth specimen was removed without injury to the pleura. The operation lasted twelve minutes, under brief ether anesthesia. Examination of the specimen showed large islands of marrow cells with active hemopoiesis. Leukogenesis still predominated over erythrogenesis; however, the latter had definitely increased over that in the second and third specimens. This specimen showed a marked contrast to the first specimen; the marrow core was almost a solid mass of active marrow cells; the bone septums were few and thin, and the marrow islands were all confluent into a solid core. The vascularity was graded 3, activity 3, erythrogenesis 2, leukogenesis 2 to 3, and density 2 to 3. The definite increase in erythrogenesis was now equal to the leukogenesis.

October 4 a review examination of the four specimens was made with a special bifocal microscope. The notes and drawings are omitted because the findings essentially corroborated those of former examina-tions.

November 4 the dog weighed 7.8 kg.; its condition was good. The erythrocytes numbered 5,070,000, the leukocytes 15,800, and the hemoglobin was 50 per cent. November 5 the fifth specimen was removed. Examination showed an active, dense mass of marrow cells. The vascularity was graded 3, activity 3, erythrogenesis 3 to 4, and density 3. Three other slides of the same specimen gave the same formula.

January 28, 1920, the dog weighed 8.3 kg.; it was thin and listless, but the wounds had healed without infection. The erythrocytes numbered 3,610,000, the leukocytes 24,300, and the hemoglobin was 50 per cent. The sixth specimen was removed from a point midway between the spine and sternum. Examination showed the marrow less active than that of the fifth specimen. There was slight fibrosis. The vascularity was graded 3, activity 2 to 3, erythrogenesis 2 to 3, leukogenesis 2, and density 2 to 3.

April 21 the dog weighed 9.9 kg.; its condition was good. The erythrocytes numbered 3,800,000, the leukocytes 28,000, and the hemoglobin was 58 per cent. April 22 the seventh specimen was removed. Examination showed large marrow cell islands, active and dense. The bone cortex was still quite thick, but it had been much honeycombed by small islands of marrow cells. The vascularity was graded 3, activity 3, erythrogenesis 3, leukogenesis 3, and density 3.

July 13 the dog weighed 9.4 kg.; its condition was good, although it was anemic. The erythrocytes numbered 4,790,000, the leukocytes 13,950, and the hemoglobin was 68 per cent. July 15 the animal was etherized and an immediate necropsy performed. Specimens of rib marrow from numerous places, all midway between the spine and the sternum, specimens of central femur marrow, the hemolymph nodes, the mesenteric and axillary lymph nodes, and the liver were all sent to the laboratory in Zenker's solution. The hemolymph nodes seemed to be slightly hypertrophied, the largest was 4 mm. in diameter. The thorax was free from adhesions and signs of infection; the pleura was smooth and shiny everywhere in spite of the numerous rib resections. The animal seemed to be entirely recovered from the severe anemia. The vascularity of the eighth specimen was graded 2, activity 3, erythrogenesis 2 to 3, leukogenesis 2 to 3, and density 2.

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CLINICAL DIAGNOSIS BY THE AID OF VISCOSIMETRY OF THE BLOOD AND THE SERUM WITH SPECIAL REFERENCE TO THE VISCOSIMETER OF W. L. HESS*

MAX E. BIRCHER

The viscosimeter of Hess is based on the law of Poiseuille that fluids at equal temperature and equal pressure, passing through capillary tubes of equal caliber, vary in their rate of flow in direct proportion to their internal friction; that is, their viscosity. The law can be applied only when liquids are driven through the capillaries by a certain pressure. This pressure should be moderate so as to obtain a gentle flow of the liquid, but it must be greater than the force of gravity.

By the aid of a strong rubber bulb blood and distilled water are drawn simultaneously under the same pressure through two capillaries. If the capillaries are of equal length and lumen, and if the temperature, pressure, and time are the same for both capillaries, the flow through volume of two liquids is inversely proportional to the viscosity. The volume is measured by a graduated glass tube, and the volume of water taken as a standard. The flow through volume of any fluid of a greater viscosity than water will be smaller than that of water, or the flow through volume of water will be just as much larger as the tested fluid is more viscous. If blood is sucked from 0 to 1 the water column reaches a point in the graduated tube which indicates how much farther the water flowed under the same conditions. At this point a reading is taken which represents the viscosity of the blood compared with water, and is, therefore, relative.

The viscosity of fluid is expressed in viscosimetric units of distilled water at a temperature of 20 C. Temperature readings should be between 17 and 23 C., and a satisfactory correction can be made by subtracting 0.8 per cent of the reading for every degree below and by adding 0.8 per cent for every degree above.

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* Abridgment of paper published in full in the Journal of Laboratory and Clinical Medicine, 1921, vii, 134–147. From the Section on Medicine and Clinical Pathology, Mayo Clinic.

The original article contains a detailed description of the Hess viscosimeter, instructions as to its use, and the preparation of the patient.

VALUE OF THE DETERMINATION OF VISCOSITY

Viscosity is a body constant, like temperature, and, in the same individual, remains the same, including daily variations, over long periods. Normal viscosimetric values as a standard for comparison (after Hess) are:

TABLE 1

	Viscosimetric rates.	
Age.	Males.	Females.
0 to 10 years	3.8	3.8
11 to 20 years	4.4	4.2
21 to 35 years	4.7	4.2
36 to 50 years	4.9	4.4
51 to 81 years	4.6	4.5

Normal viscosimetric values of serum range from 1.7 to 2.0 (plasma from 0.2 to 0.3 higher).

Practically the most important factors which contribute to the complex value of the viscosity of the blood are the serum and the cellular elements. Experiments carried out by the author in 1919 in the Hess laboratory clearly demonstrate the influence of dissolved protein in the serum. The delicacy of the method was proved by the fact that differences of the protein were readily revealed, and that it was possible to differentiate protein by a so-called viscosimetric index. Other experiments specified the influence of the volume of red blood cells on the viscosity of the blood, at least viscosimetry was shown to give an exact determination of cell volume (Ulmer-Bircher method).

CELLULAR ELEMENTS

Red cells.—Viscosity is directly related to the total volume of red cells. In pernicious anemia the size of the red cells does not permit the viscosity to decrease in proportion to the low count, while in secondary anemia the viscosity is very low. This indicates that the megalocytes in pernicious anemia must be much more prevalent than has been believed.

White cells.—These cells, except in pathologic conditions such as the leukemias, are present in too small numbers to be a factor.

THE DETERMINATION OF THE ALBUMIN AND GLOBULIN PERCENTAGE IN THE SERUM

In discussing the viscosity of the serum as a factor of the total value it has been mentioned that viscosimetry furnishes approximately the percentage of protein content of the serum. Large series of experiments have shown that there are discrepancies which can only be explained by differences in viscosity of various proteins, because for the same amount of protein different viscosimetric values have been obtained. It has been shown that protein consists of two substances of different viscosity, albumin and globulin, the former less viscous than the latter. Heyder and Rohrer have established a definite relation among the three factors: viscosity, protein percentage, and albumin-globulin mixture. They established the viscometric curve of albumin solutions of different concentration and one of globulin solutions under the same conditions. The albumin and globulin curves determine a field which includes all possible rates of any mixture of globulin and albumin. The important part of this field is reproduced in Fig. 171, by means of which it is possible to interpolate the unknown factor, the albumin-globulin mixture in percentage. Naegeli has made observations on the albumin-globulin relation, and finds for normals that the serum protein is 60 to 80 per cent albumin and 20 to 40 per cent globulin. He has made observations also on muscular activity, the newborn and the parent, food intake, arterial and venous blood, hunger, chlorosis, pernicious anemia and secondary anemia.

THE DETERMINATION OF THE TOTAL BLOOD CELL VOLUME AND THE EXACT VOLUME OF A SINGLE RED CELL

A hyperbolic curve was obtained in measuring the viscosity of blood samples which were so arranged that the first consisted of serum only and the following samples had a steadily increasing amount of suspended red cells. With serums of higher protein concentration similar curves were almost absolutely parallel with the first one.

To determine the total cell volume it is only necessary to know the viscosity of the blood and the viscosity of the plasma. The viscosity of the plasma $\eta 2$, indicates which curve has to be chosen (point $\eta 2$) and the viscosity of the whole blood η will be found lying on this curve. The corresponding point on the abscissa indicates the percentage of the cells. By an easy interpolation it is possible to cover every case.

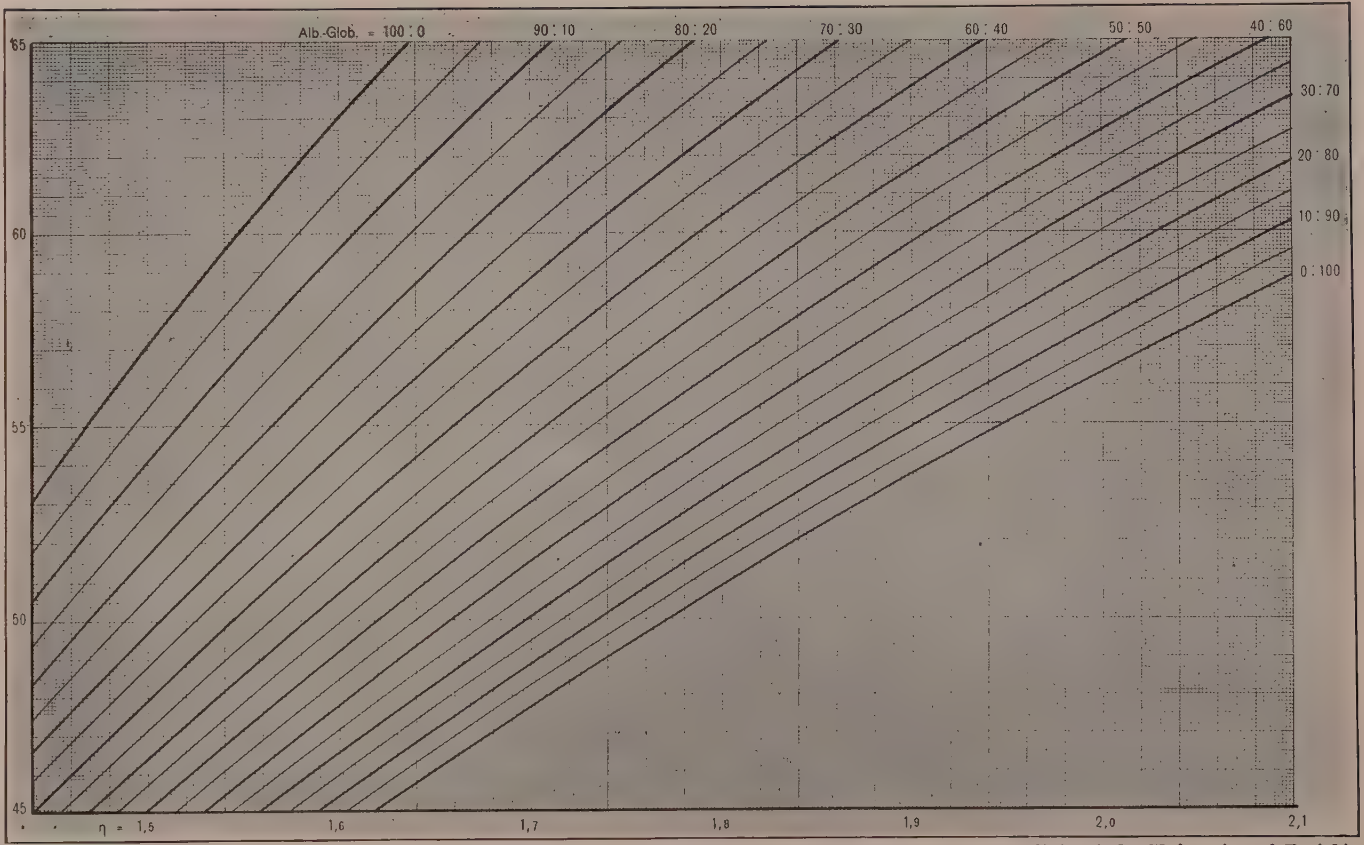

FIG. 171.—Viscosimetric and refractometric function of albumin-globulin mixtures (Chart used at the clinic of the University of Zurich). This chart allows the interpretation of an unknown mixture of albumin and globulin when the viscosity and the refraction of the serum have been determined.

To get the volume of one red cell, divide the value of the total volume of red cells in 1 c. mm. by the number of cells.

SUMMARY

The value of determining the viscosity is threefold.

1. In circulatory questions, viscosity should be considered. Red cells and viscosity are the two opposite factors which have a determining influence on the effect of heart work.

2. The viscosimetric factor is an excellent check of the normal blood test, because it depends on the different constituents of the blood; it is a delicate indicator for changes in their relation, and on this fact is based some valuable diagnostic information.

3. The viscosity is an accurate means of analyzing the constituents of the blood; the quantity and quality of protein dissolved in plasma may be studied as well as the exact volume of the cellular elements. On these determinations are based the diagnostic applications supported by Naegeli.

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THE GLOBULIN CONTENT OF THE BLOOD SERUM IN SYPHILIS*

MAX E. BIRCHER AND ALBERT R. McFARLAND

Bircher and McFarland have presented the results of their study of the globulin content of syphilitic patients and the effect of treatment upon it. They used the method of Naegli in their determinations which consists of a combination of refractometry and viscosimetry. This method they believe superior to others because of its simplicity and accuracy and the short time required to make the determinations.

In about 90 per cent of syphilitic patients the globulin content of the blood serum was found to be high; that is, more than 50 per cent. When treatment with salvarsan and mercury was begun the globulin rates gradually declined. After about five or six salvarsan injections at weekly intervals the globulin was usually reduced to normal. The same figures were obtained as a rule in patients who had previously had a series of arsphenamin treatments so that the reduction of the globulin is not permanent.

It is suggested that a determination of the time at which this increase begins between courses of treatment may serve as an indicator of how long the rest periods should be in treating syphilis.

The globulin determination is not a specific test since the globulin content is often found to be increased in certain types of tuberculosis and perhaps in other conditions. It is to be looked on as one of the nonspecific defense mechanisms of the body rather than as a specific test.

* Abstract of paper published in full in the Archives of Dermatology and Syphilology, 1922, v, 215–233. From the Section on Dermatology, Syphilology, and Clinical Pathology, Mayo Clinic.

II. ON THE VALUE OF THE REFRACTO-VISCOSIMETRIC PROPERTIES OF BLOOD SERUM IN CANCER*

MAX E. BIRCHER

Bircher reports the result of studies on the refractivity and viscosity of blood serum in cancerous patients as compared with patients having benign tumors and with normal controls. He found that the refracto-viscosimetric quotient in normal patients was 331, in patients with benign tumors 328, while, in patients with malignancy, the quotient

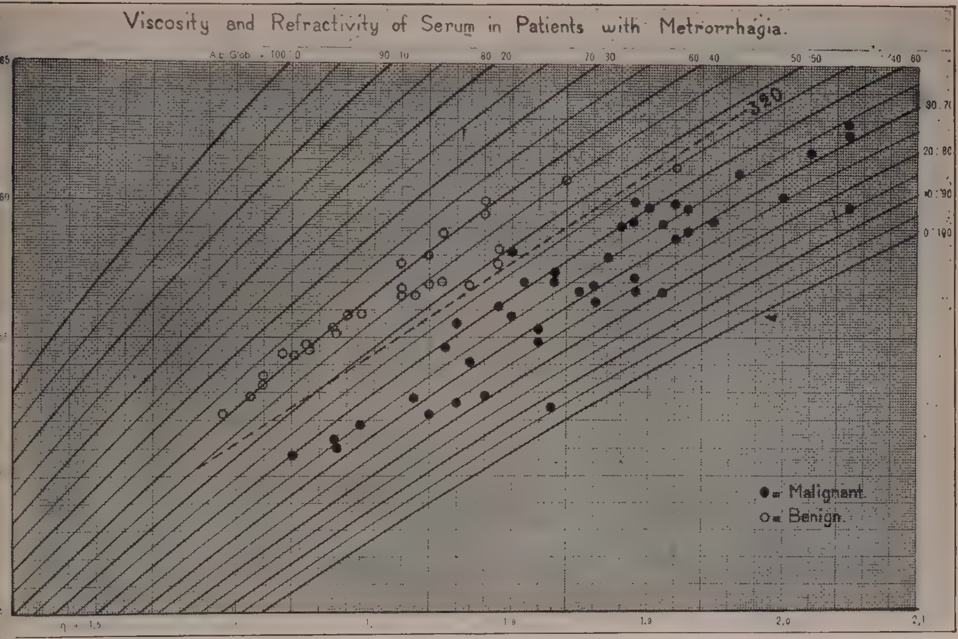

Fig. 172.

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* Abstract published in full in the Journal of Laboratory and Clinical Medicine, 1922, vii, 660–664. From the Section on Medicine, Mayo Clinic.

is decreased to 307. The method of computing the quotient and the technic is described.

The first series of experiments proves the validity of the technic and demonstrates the great constancy of the refracto-viscosimetric quotient under normal conditions. The pathologic material gives evidence of marked change in the physical findings in the serum. While benign tumors do not affect the blood, any form of cancer causes a definite alteration. This can best be expressed by the refracto-viscosimetric quotient which, in normal conditions, is almost always above 320, and in malignancy below 320, as shown in Figure 172.

III. THE VALUE OF THE REFRACTO-VISCOSIMETRIC PROPERTIES OF BLOOD SERUM IN CASES OF TUBERCULOSIS*

MAX E. BIRCHER

In order to observe the viscosity and refractivity of blood serum in cases of tuberculosis 160 patients at Glen Lake Sanatorium were studied.

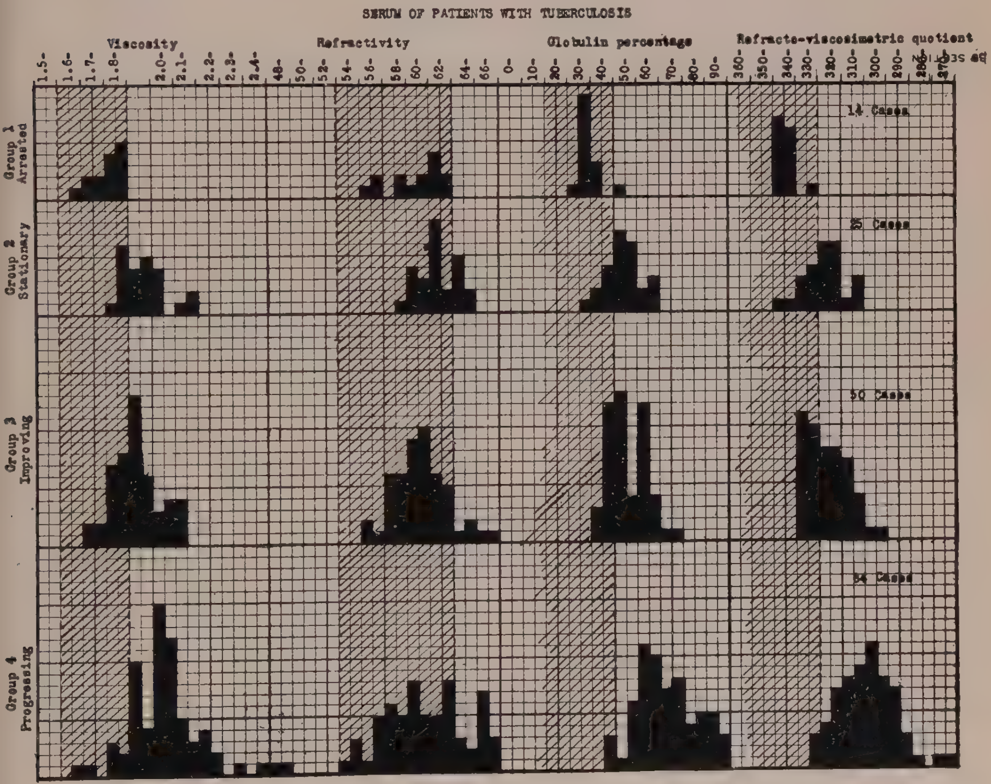

FIG. 173.

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* Abstract of paper published in full in the Journal of Laboratory and Clinical Medicine, 1922, vii, 733–735. From the Section on Medicine, Mayo Clinic.

The cases were divided into four groups, according to the stage of the disease: (1) arrested cases with no signs of active tuberculosis for at least three months, (2) stationary cases, (3) cases in which there was improvement, and (4) cases in which the signs of activity were progressing. The groups are divided in the chart by horizontal lines and subdivided by vertical lines (Fig. 173).

Viscosity is expressed in relation to the viscosity of distilled water; refractivity is expressed in the units of Pulfrich. Globulin percentage was obtained by interpolation with the aid of Naegeli's chart. It illustrates the fact that serum, especially its colloidal component, with a certain refractive power, may vary in viscosity. Two serums, for example, were obtained with a refractive index of 60.0 (Pulfrich units). One showed a viscosity of 2.00, the other 1.80. The refracto-viscosimetric quotient is 300 in the first sample and 333 in the second; the higher the quotient, the lower the viscous power of a certain colloid substance. The normal range in each condition is represented by the shaded area in the chart. The height of the black columns indicates the number of cases.

DISCUSSION

The viscosity is normal in arrested cases. The refractivity of tuberculous serum is normal in most cases. The albumin-globulin ratio is shown in the third column in the chart. The globulin is high, especially in progressive cases. The refracto-viscosimetric quotient indicates that in tuberculosis the viscosity of the serum is abnormally high in relation to refractivity.

THE IMPORTANCE OF VISUALIZING ESTABLISHED SCIENTIFIC DATA WITH REFERENCE TO THE SIZE OF THE BODY CELLS AND THEIR CHEMICAL SUPPLIES IN THE CIRCULATING BLOOD*

GEORGINE LUDEN

The author discusses the value of visualizing, through comparison with familiar quantities and measures, the size of the body cells, the total blood volume, the total number of leukocytes and erythrocytes in the circulation, and the total amounts of iodin, urea, sugar, natrium chlorid, and other chemical blood constituents. The relative size of electric ions and the concentration in which epinephrin is physiologically active are also considered.

The size of one millimeter may be visualized by dropping the point of a soft pencil on paper; the resulting dot measures one millimeter. One cubic millimeter, this dot in three dimensions, contains, in blood counts, six to ten million leukocytes, or four to five million erythrocytes.

The total number of leukocytes in the circulation of an adult weighing 154 pounds with a total blood volume of 5,000 c.c., or slightly more than one gallon, is no less than thirty billions. The most rapid counting of seven billion dollars will take one person at least 400 years. The total amount of sugar in the total blood volume of a 154 pound adult just equals one medium teaspoonful (4 to 6 gm.) and the total amount of iodin in the circulation is merely 1/100 of a grain or the "average dose" of atropin or hyoscin. The strip of intestine or uterus used in bio-assay by Stewart and Rogoff "detected" the presence of epinephrin in a concentration of one in three hundred and thirty millions and furnished graphic records of this concentration which may be visualized by diluting 10 c.c. of whisky with the total content of 1320 city sprinkling carts.

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* Abstract of paper published in full in Endocrinology, 1921, v, 715–728. From the Section on General Pathology, Mayo Clinic.

The foregoing and other data furnish food for thought in connection with the "average dose" in which the preparations of the Pharmacopeia and Organotherapy are often prescribed; their bearing on the relation of combustion products, including carbon monoxid, to the cancer problem and other medical problems is discussed.

STUDIES IN BLOOD CHOLESTEROL IN SYPHILIS*

ALBERT R. McFARLAND

The study was made for the purpose of determining any possible relation between blood cholesterol values and the serologic findings, and the clinical manifestations of syphilitic infections. A brief sketch is given of the chemical composition, physical properties, source, occurrence, and function of cholesterol in the body.

Among other work cited is that of Wilensky and Rothchild on gallbladder disease, in which they found cholesterol values to be of very little importance, except perhaps in making a differential diagnosis of obstructive and catarrhal or cirrhotic jaundice. Kipp's investigations on pneumonia and Henes' on nephritis seemed to indicate that a definite relation exists between these diseases and cholesterol determination. Schnobel, in his study of gastro-intestinal disorders, was unable to demonstrate any relationship of diagnostic value.

More than 100 patients with syphilis were studied from the standpoint of their serologic response to treatment, their clinical response, the amount and recency of treatment to the cholesterol determinations, and the type of syphilitic involvement. Bloor's technic, which is described in full, was used.

CONCLUSIONS

1. The positive serum Wassermann reaction apparently does not depend on a high cholesterol value in the blood. While it is interesting to corroborate this fact, it is not surprising in view of the probable complexity of the Wassermann reaction.

2. Cholesterol values in syphilitic patients in general tend to be medium and low rather than high. Occasional high values might possibly be explained on some other basis; the problem has been confined to syphilis, and no pretense has been made of studying the choles-

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* Abstract of paper published in full in the Archives of Dermatology and Syphilology, 1922, vi, 39–49. From the Section on Dermatology and Syphilology, Mayo Clinic.

terol activity in the body. While this may mean that cholesterol as a defense agent is low in a chronic disease like syphilis, just as leukocytosis is low in chronic infections, yet from the practical standpoint it does not appear that cholesterol determinations in the series, with the possible exception of central nervous system cases, have given results much different from those to be expected from a similar series of patients without syphilis.

3. The amount of arsphenamin received and the time elapsed since its last injection do not have any obvious effect on cholesterol values. Cholesterol may be a defense agent in syphilis, but in most cases it was not detected in greater amount than might be expected in a series of average patients without syphilis, and hence it is not affected materially by treatment for syphilis.

4. The majority of syphilitic patients have a low or a normal difference between the Bloor I and the Bloor II tests, while only a few have a high difference.

5. There is apparently no relation between the cholesterol values and the clinical and serologic response of the patient.

6. The only recognizable relation between the clinical type of syphilis and blood cholesterol values is the large proportion of high cholesterol estimations in syphilis of the central nervous system.

A STUDY OF MICROLYMPHOIDOCYTIC LEUKEMIA*

SOLOMON FINEMAN

A case of leukemia was studied in which there were enormous numbers of "micromyeloblasts" in the circulating blood. Ordinarily a diagnosis of micromyeloblastic leukemia would have been made. Clinical evidence, however, pointed to lymphopoietic activity. There was marked enlargement of the mediastinal shadow, lymph nodes, and spleen.

Transfusions totalling 2,760 c.c. of blood for a period of two months had no influence on the steadily progressing anemia. Before death the majority of erythrocytes were of normal morphology and were probably transfused. The leukocytes showed extraordinary sudden fluctuations. Numerous mitotic cells were present in the circulating blood. Very marked fluctuations in the size of the spleen, lymph nodes, and mediastinal shadow were observed.

The lymphoidocytes of Pappenheim (myeloblasts of Naegeli) or stem cells were present in the blood during seventy-five days of daily observation. They varied greatly in size. The majority were smaller than the average erythrocyte, others were as large as mononuclears. Stained with Wright's stain they were identical in morphology with the cells described and shown by Pappenheim. Their cytoplasm was basophilic and scant in amount. The majority of cells did not contain azure granules. The nuclear chromatin formed a very fine, evenly distributed, sieve-like meshwork in contrast to the large clumped chromatin blocks of the lymphocytes.

Numerous transitional forms between these stem cells and lymphocytes were present in the blood. Some myelocytes and nucleated erythrocytes were present, probably associated with the anemia.

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Arts, 1921. Published in full in the Archives of Internal Medicine, 1922, xxix, 168–220. From the Departments of Animal Biology and Medicine, University of Minnesota, Minneapolis.

A study of 200 sections of a lymph node obtained by biopsy, fixed in Helly's fluid and stained with Dominici and methyl-green pyronin showed that the stem cells were proliferating in large numbers in the capsule, interfollicular tissue, lymph cords, lymph follicles, and in the germ centers of the lymph follicles.

Transitional forms between the connective-tissue cells of the capsule and the stem cells, and between lymphocytes and these stem cells, were present in the capsule. In the interfollicular tissue, in the follicles, and even in the germinal centers transitional forms between the stem cells, reticulum, and lymphocytes were present.

The lymph follicles and lymph cords showed no signs of atrophy, but showed every evidence of marked activity. Mitotic figures were numerous. The only signs of atrophy or necrosis were found in the capsule.

The stem cells formed the majority of the cells of the parenchyma. They also constituted by far the majority of the cells in the lymph sinuses and were very numerous in the blood vessels of the node.

From the morphologic evidence at hand the conclusion is justified that in all probability the majority of the micromyeloblasts of the blood were coming from the lymphoid organs, not only from the portions, which according to the dualists may give rise to myeloid cells, but from the sanctum sanctorum of the lymphoid tissue, namely, the follicles and germ centers.

The data in this case, when considered in conjunction with a fair amount of evidence produced by others, would seem to show that the dualistic and polyphyletic theory of the origin of blood cells does not always hold true.

POSTOPERATIVE THROMBOPHLEBITIS*

HENNING F. B. WIESE

Next to infection in the wound and inflammation of the lungs, thrombophlebitis closely associated with pulmonary embolism is one of the most common postoperative complications.

Thrombosis consists of the coagulation of the blood in the vessels during life. The clotting is brought about by the transformation of fibrinogen into fibrin and fibrinoglobulin under the influence of thrombin. The blood's thrombogen (prothrombin) is activated by thrombokinase in the presence of lime salts. Thrombokinase is probably derived from the leukocytes and the platelets.

Howell's theory of coagulation is based on the disturbance of balance between prothrombin and antithrombin. This is brought about by thromboplastin, a substance given off by injured tissues or cells. Thromboplastin neutralizes the antithrombin and frees prothrombin, which, by the aid of calcium, can form thrombin.

In thrombosis the formation of fibrin is always preceded by the agglutination of cells (platelets) after the latter have suffered some injury.

One hundred six cases of postoperative thrombophlebitis occurring in the Mayo Clinic in 1919 and 1920 form the basis of this investigation. In ninety-six of these a diagnosis of thrombosis, or thrombophlebitis of the lower extremities after operation was made. In ten cases which had been diagnosed pulmonary embolism, the thrombophlebitis was discovered at necropsy. One case of pulmonary embolism was that of a patient who died eight hours after a cholecystectomy for acute suppurative cholecystitis.

Seventy-eight of the 106 patients were females, and twenty-eight were males. This may be explained by the larger number of laparotomies performed on women.

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* Abridgment of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, 1922. From the Section on Surgery, Mayo Clinic.

ETIOLOGY

Von Recklinghausen believed in the "individual disposition" of the venous system for the formation of the thrombi as the cause of thrombophlebitis. Other theories that have received consideration are the mechanical and the infectious theories.

Direct infection of the wall of the veins from the outside may take place during an operation or as a result of operation. However, thrombophlebitis seems to be as common after a so-called clean operation, as after operations in infected areas. Statistics from the War seem to show few cases of thrombophlebitis in spite of the severity of injuries and the septic character of wounds of the lower extremities.

In the Mayo Clinic where wounds are carefully grouped it has been found that thrombophlebitis is most common in the cases in which there was possibility of infection during operation from the opening of bile ducts, stomach, intestines, and so forth, and in which drainage was not instituted.

In operations on the vagina and rectum and in cases of sepsis the incidence was also high. Wound infection after operation occurred often in this series. Infection of the endothelium of the vessels from the blood seems probable, causing the primary injury to the wall, allowing the production of the thrombokinase or thromboplastin (MacCallum). The fever and local tenderness, accompanying thrombophlebitis, and the increased number of cases during epidemics of infectious diseases seem to favor the infectious theory.

Mechanical obstruction and the slowing down of the blood stream is considered of great importance by certain observers. Considerable stress is laid on the formation of "eddies" at the valves of the veins. Because thrombophlebitis is more common in persons over forty the mechanical theory receives considerable support. It is supposed that the circulatory disturbances are the result of a weakened heart. Apparently this complication occurs more often after operations below the diaphragm (especially laparotomy), than after any other operations. The normal movements of the diaphragm influence the circulation in the subphrenic vein-trunks. After a laparotomy the patient, in order to immobilize the wound, resorts to the typical high costal breathing, thus diminishing the influence of the diaphragm on the return of the venous blood through the inferior vena cava. This means a slowing of the blood stream with increased chance of thrombus formation.

Capelle asserts that most of the cases occur between the tenth and twentieth day after operation, simultaneously with the resumption of the abdominal type of respiration. Eighty-one of the 106 patients in this series had laparotomies (counting those for umbilical and ventral hernias, and operations on the kidney, ureter, and bladder).

An argument in favor of the mechanical theory is the fact that the thrombosis has its sites of predilection in the veins of the lower extremities and the pelvis. If infection were the main cause, one would expect to find this complication after operations in other regions of the body as well.

Other etiologic factors must be considered, namely, changes in the walls of the vessels as a result of age; changes in the blood (during pregnancy or after the influence of certain poisons), and the effect of an inhaled anesthetic. In most of the cases in this series ether was used; in four, local anesthetic (novocain).

Varicose veins of the lower extremities are thought to play an important part. These varicosities are not always a sign of the lowered power of the heart. Varicose veins were mentioned in the histories of fifteen cases in the series, ten women and five men.

In this series thrombosis occurred on both sides in twenty-five cases, on the left in forty-four, on the right in twenty-eight. In nine cases the side involved was not mentioned.

The frequency of involvement of the veins of the left leg has supposedly been due to the less favorable circulatory conditions in the left side, namely, pressure from the crossing of the three arteries, the common iliac, the middle sacral, and the left hypogastric; the smaller angle of outlet of veins into the inferior vena cava, and emptying of the left spermatic veins into the left renal vein, instead of directly into the inferior vena cava as they do on the right.

Although thrombophlebitis occurs in every month of the year, there was a decided increase in this complication during the epidemic of influenza early in 1920. This seems to suggest a close relationship between infections and thrombophlebitis.

Previous diseases.—Forty-four of our patients had had influenza (grippe); thirty tonsillitis, nineteen pleurisy, and eighteen rheumatism. The incidence of other previous diseases was lower.

Previous operations.—Seven of our patients had had laparotomies for pelvic disease, six perineal and cervical operations; six curettements; six rectal operations; five operations on the kidney, ureter, or bladder; four on the gallbladder; four transfusions (three one day before operation, one four to ten days before); three tonsillectomies; three appendectomies (one followed by postoperative thrombophlebitis); one abdominal paracentesis; one operation for vesicovaginal fistula; one resection for carcinoma of the rectosigmoid; one induced abortion (six months) for toxemia; one thyroidectomy; one herniotomy, and one incision and drainage of the leg.

Thirty-four of our patients had lost from 6 to 50 pounds. There was slight loss of strength in thirty-five. A moderate hypertension was found in most patients as one might expect because of their age. Forty-three patients had systolic blood pressure of 140 to 226, twenty-seven, 145 and higher, and fifteen above 155. Low systolic pressure was rare.

Thirteen patients had hemoglobin percentages of 30 to 60; fourteen had less than 4,000,000 erythrocytes; seventeen had leukocytes of more than 10,000, the highest being 20,200.

General findings.—In view of the theory of infection as the cause of the disease, the low percentage of infectious conditions is interesting. Infections at the time of operation, not including chronic pelvic infection or cholecystitis included one case each of acute gangrenous appendicitis (with peritonitis), acute cholecystitis associated with infected hydronephrosis, pyonephrosis with perirenal infection, recent epididymitis, pyometra, gangrene of the foot, varicose ulcer of the leg, ulcerating carcinoma of the breast, bed-sore, chronic osteomyelitis, and permanent sinusitis. In the routine examination chronic tonsillitis was revealed in forty-eight cases and septic teeth in sixty-two.

The incidence of impaired function of the heart was low; fourteen patients had a systolic murmur at the apex, pulmonary, or aortic areas; three had cardiac hypertrophy. Edema was noted in fifteen cases; it was quite marked in four. Tortuous arteries were mentioned in five cases. Forty-four of the patients were fleshy and eleven thin.

Onset of symptoms.—Postoperative thrombophlebitis developed in the majority of cases from seven to twelve days after operation. Twenty-four of the patients had not been out of bed when they began to have symptoms. Thirteen showed the first sign of thrombosis on the first day they were up; four on the second, sixteen on the third, nine on the fourth, ten on the fifth, three on the sixth, five on the seventh, two on the eighth, and one each on the ninth, tenth, eleventh, and thirteenth days.

Symptoms.—Pain, edema, and tenderness are the most important symptoms. Pain in the ankle, calf, popliteal space, thigh, along the saphenous and femoral veins, and in the groin or hip was mentioned in sixty-five cases. Edema of the ankle, foot, calf, thigh, or groin was found in twenty-nine cases. Tenderness on pressure in the calf, along the saphenous or femoral veins, or in the groin was recorded in fifty-one cases. A tender lump in the groin or calf of the leg with induration along the saphenous vein was complained of in eight cases. Thickened vessels were palpable in eight cases. Chills were noted in three cases. The leukocytes in four cases numbered from 11,800 to 28,400. Ecchymosis was discovered in one case; local heat and redness were mentioned in several cases, and cyanosis of the leg was a symptom in a few.

Temperature was increased in fifty-eight cases. It ranged from 101 to 103 in nine cases, from 100 to 101 in nineteen, and from 99 to 100 in thirty; it lasted for from one to fourteen days. In some of these cases other complications, such as infected wounds or pulmonary disturbances, may have caused the rise of temperature.

Table 1 shows the frequency of thrombophlebitis after gynecologic operations, and its relative rarity after such an operation as gastro-enterostomy. The amount of trauma to the tissue in these cases because of handling may be an important factor; the question of the relative youth of patients with ulcer may also be of some consequence.

The side on which operation is performed seems to have little influence on the thrombus formation. Sixteen of the twenty-five cases of salpingectomy or salpingo-oöphorectomy were bilateral. In these the thrombosis was on the right side in three cases, on the left in ten, and bilateral in three. The thrombosis was on the right side in one of the three cases of right salpingectomy, on both sides in one, and not mentioned in one. The thrombosis occurred on the right side in three of the six cases of left salpingectomy, on the left side in one case, and on both sides in two cases. Twelve of the patients on whom appendectomy was performed had thrombosis on the right side, thirteen on the left side, and seven on both sides.

In the two cases of right inguinal herniotomy, one patient developed thrombosis on both sides and one on the right side; in one case of left herniotomy thrombophlebitis developed on the right side; in one case of bilateral herniotomy thrombosis developed on the left.

Many of these patients were considered poor surgical risks; 20.8 per cent were operated on for malignant disease. In certain cases the operative risk was considered as high as 20 per cent.

Convalescence.—The convalescence in many cases was slow. About

TABLE 1

Operations in 105 Cases of Postoperative Thrombophlebitis

	Cases.	Total cases.
Total abdominal hysterectomy	....	14
with salpingo-oöphorectomy	12	
with appendectomy	9	
Subtotal abdominal hysterectomy	....	14
with bilateral or unilateral salpingectomy or salpingo-oöphorectomy	11	
with appendectomy	3	
Myomectomy	....	2
with right salpingectomy, oöphorectomy, and appendectomy	1	
with appendectomy	1	
Cholecystectomy (alone)	....	16
with appendectomy	12	
with choledochotomy	2	
with excision of duodenal ulcer	1	
Excision of duodenal ulcer and appendectomy	1	1
Excision of gastric ulcer and gastro-enterostomy	1	1
Gastro-enterostomy and appendectomy	1	1
Partial gastrectomy (alone)	4	5
with appendectomy	1	
Appendectomy (one gangrenous appendix with purulent peritonitis)	2	2
Abdominal exploration	2	2
Abdominal paracentesis and appendectomy (tuberculosis)	1	1
Moschcowitz's operation for prolapse of rectum, appendectomy, and intraperitoneal shortening of the round ligaments	1	1
Dilatation and curettement (alone)	2	6
with inguinal herniotomy	1	
with cautery to cervix, appendectomy, and intraperitoneal shortening of round ligaments	1	
with perineorrhaphy, trachelorrhaphy, and an external Alexander operation	1	
with removal of cervical polyp	1	
Intraperitoneal shortening of round ligaments, appendectomy, operation for umbilical hernia, amputation of cervix, and perineorrhaphy	1	1
Perineorrhaphy and Bovee operation for cystocele (one of them also ventrofixation)	2	2
Packed for threatening abortion	1	1

TABLE 1—*Continued*

	Cases.	Total cases.
Vaginal hysterectomy (alone)	2	5
with perineorrhaphy	3	
Operation for carcinoma of sigmoid	1	1
Colostomy	1	1
Posterior excision of rectum (alone)	1	3
with colostomy	1	
with colostomy as a secondary operation	1	
Resection of bladder for carcinoma	1	1
Suprapubic prostatectomy	4	4
Nephrectomy	1	1
Pelvic nephrotomy	1	1
Exploration of kidney by trocar	1	1
Ureteropelvic plastic operation	1	2
Cystoscopic examination	1	
Operations for hernia	....	6
ventral	1	
umbilical, and ileostomy three days later	1	
inguinal	2	
bilateral inguinal and appendectomy	1	
inguinal, hydrocele operation and appendectomy	1	
Thyroidectomy for multiple adenomas in colloid goiter (alone)	1	2
with inguinal hernia	1	
Radical amputation of the breast for carcinoma	3	3
Operation for varicose veins	1	1
Amputation of the leg	1	1
Exploration for chronic osteomyelitis	1	1
Manipulation and reduction of fractured hip	1	1

twenty patients reported by letter that for from two to six months after the operation they were bothered with aching of the feet, and weakness, stiffness, pain and swelling of the leg, or edema of the ankle, especially after walking. In one case an ulcer of the leg developed seven months after operation; the legs had been painful and tender since the thrombophlebitis began. The most dreaded end-result of thrombophlebitis is pulmonary embolism.

While many cases of sudden postoperative death from other causes

TABLE 2

PULMONARY COMPLICATIONS IN 106 CASES OF THROMBOPHLEBITIS

Cases.	Complication.	Onset of complication after operation.	Onset of thrombophlebitis, days after operation.
A89120	Lobar pneumonia (before thrombophlebitis)	?	9
A68854	Pain left side chest with "tightness"	15	7
A260726	Pleurisy	15	13
A339149	Pleurisy	?	?
A332740	Pleurisy	?	10
A304280	Bronchopneumonia	2	11
A117981	Rheumatism left shoulder, sudden pain left costal margin, no cough, examination of sputum negative	?	12
A339021	Pulmonary embolism	16	16
A320155	Bilateral bronchopneumonia (also septicemia)	52	13
A314666	Pulmonary embolism	21	7
A309488	Pleurisy	12	15
A303763	Sudden sharp pain in precordium; catching on inspiration, pulmonary embolism 90 per cent	29	13
A301615	Bronchopneumonia, pleurisy	13	11
A293947	Pain right side chest; painful deep inspiration, examination negative	31	9
A291012	Pulmonary embolism Lobar penumonia	7 18	25
A317356	Chill, fever; heavy feeling in chest; no cough; examination negative	27	20
A258811	Hemorrhage from perforation of aneurysm; pulmonary embolism	16	15

will be mistaken for pulmonary embolism it seems quite certain that pulmonary embolism occurs much more often than it is diagnosed, and that many cases of minor postoperative lung complications really are caused from smaller emboli which find their way into the lung tissues and often give origin to the so-called embolic pleuropneumonia, the latter characterized especially by the symptoms of involvement of the pleura rather than other forms of pneumonia.

Pulmonary complications were noted in seventeen of the 106 cases of diagnosed postoperative thrombophlebitis (Table 2).

Of the cases of this series diagnosed thrombophlebitis, pulmonary embolism occurred in at least five or six, while in several others the diagnosis was questionable and the symptoms might have been caused by a minor embolus.

TREATMENT

Prophylactic treatment is of prime importance. The patient should be in good condition, reduced in weight if very obese, and should take plenty of fluids before operation. Chemical substances, although of little value, have been used to lower the coagulability of the blood. During the operation good technic and skillful handling of the tissues is very important. Infections should be guarded against.

Following the operation it seems advisable that patients move around early, and have their physical needs attended to routinely and regularly. In the Mayo Clinic, patients with laparotomies often get up on the sixth or seventh day unless existing conditions do not warrant it. Statistics seem to show that this early activity after operation is justifiable, and may be important in preventing embolism.

Kümmel performed 610 laparotomies during 1906 and 1907, and 0.99 per cent terminated fatally, because of pulmonary embolism. After letting the patients up early (1908) he had a mortality from pulmonary embolism of 0.12 per cent.

Kronig's results of "exercise therapy" show 2,265 laparotomies with 0.6 per cent of cases of femoral thrombosis and 0.1 of fatal embolism.

The treatment of thrombophlebitis is simple. The patient should be kept in bed with the leg elevated. In the beginning an ice-bag is applied and later, heat to improve the circulation. An elastic stocking may be of help after the patient gets up.

In septic thrombophlebitis surgical treatment might be brought into play, such as incision of the phlegmon, or ligation of the superficial vein.

In the treatment of pulmonary embolism, rest and morphin seem about the most beneficial. Removal of the embolus from the pulmonary artery has been tried, but it is a desperate and practically hopeless procedure. If it is recalled that in 50 per cent of the cases of pulmonary embolism terminating fatally, death comes within ten minutes, and that in many seemingly desperate cases the patients, conservatively treated, have recovered, and if the possibility of a mistaken diagnosis is recalled (of Capelle's twenty-six cases clinically diagnosed large emboli, nine appeared at necropsy to have had a wrong diagnosis), then it would probably seem only fair to the patient to let him have his chance without operation.

POSTOPERATIVE PULMONARY EMBOLISM*

JOSEPH E. HEARD

Heard reports in detail 151 cases of pulmonary embolism which occurred at the Mayo Clinic from 1889 to 1920, inclusive. Forty-seven of these cases had been reported by Wilson in 1912. Diagnosis was confirmed at necropsy in forty-one cases, and in the remaining six the clinical diagnosis was quite clear.

The mortality from embolism in this group, based on 63,573 operations, was 0.07 of 1 per cent, or one death in every 1,352 operations. In twenty-eight of the forty-one cases reported, the location of the original thrombus was found in the field of operation or in the femoral vein. Wilson believed that following operation on the blood vessels, alimentary canal, and genito-urinary organs, evidence of emboli is more or less distinct in 1 to 2 per cent of all cases. Seventy per cent of emboli are found in the lungs at necropsy; 80 per cent are venous in origin, 10 per cent cardiac, and 10 per cent scattered or undetermined.

From 1912 to 1920 inclusive, there occurred at the Mayo Clinic 104 cases of postoperative embolism in 104,360 patients operated on. The clinical symptoms were sufficient to warrant the diagnosis in five of these who recovered. Necropsy was performed in ninety of the ninety-nine fatal cases, and the diagnosis confirmed. Embolism occurred in seventy-three of 60,755 women operated on, a ratio of 1 to 832, and in thirty-one of 43,605 men, a ratio of 1 to 1,406. In this period there were 2,654 deaths following operation; ninety-nine of these were due to embolism, 3.7 per cent. Operations in which postoperative embolism occurred three or more times are listed in Table 1.

The oldest patient with pulmonary embolism was eighty-two years, and the youngest six years. The average was fifty-three years. Fifty-one of the 104 were in good physical condition when operated on, thirty-seven in fair condition, and sixteen in poor condition. The anesthetic was ether in ninety-nine cases, novocain in two, cocain in two, and

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* Summary of work conducted under Dr. Walter E. Sistrunk in Section on Surgery, Mayo Clinic.

TABLE 1

OCCURRENCE OF PULMONARY EMBOLISM IN VARIOUS OPERATIONS FROM 1912 TO 1922

	Number of operations.	Cases of pulmonary embolism.	Incidence.
Abdominal exploration for carcinoma	190	4	1 to 47
Resection of rectum	594	3	1 to 183
Abdominal hysterectomy	3,751	18	1 to 208
Resection of stomach	934	4	1 to 233
Prostatectomy	1,313	4	1 to 328
Vaginal hysterectomy	1,594	4	1 to 398
Gastro-enterostomy	5,056	9	1 to 561
Salpingectomy and oöphorectomy	2,404	4	1 to 601
Cholecystectomy	9,344	15	1 to 622
Amputation of breast	2,624	3	1 to 874
Inguinal herniotomy	3,313	3	1 to 1,104
Appendectomy	8,944	4	1 to 2,237
Thyroidectomy	14,911	3	1 to 4,970

combined novocain and ether in one. Only seventy-four of the 104 patients had had hemoglobin readings. Fifty-three of these had a hemoglobin of 70 per cent or more, fourteen had a hemoglobin between 50 and 70 per cent, and seven had a hemoglobin below 50 per cent. The longest time between operation and death was fifty-eight days, the shortest time six hours, and the average ten days. In thirty-three cases the time between the first appearance of symptoms of pulmonary embolism and death was recorded. Eleven of the thirty-three patients lived more than an hour after symptoms developed; one lived three days, one lived one day, and two lived twelve hours. Most patients lived only ten to thirty minutes after the appearance of symptoms.

Thirty-four of the ninety-nine cases in which necropsy was performed showed a gross thrombosis of veins other than the pulmonary vessels. The most common site was the iliac veins, in which thrombosis occurred in seventeen instances, nine times on the left, five times on the right, and three times on both sides. In seventy-one cases the pulmonary embolus was bilateral, or occluding the pulmonary artery, and in twenty-nine cases it was unilateral.

Cases of pulmonary embolism are usually classified in three groups:

Group 1.—Patients in whom there is immediate death when only a small portion of the pulmonary circulation is obstructed.

Group 2.—Patients who die within a few minutes after symptoms appear, as a result of more or less blocking of the pulmonary circulation.

Group 3.—Patients whose death is delayed hours and in some instances for from two to three days; in these cases death is the result of an increase by thrombosis, of the blocking of a portion of the pulmonary circulation, starting with an embolism.

In the usual picture of postoperative pulmonary embolism convalescence has been uneventful. Usually within the first or second week after operation the patient suddenly feels faint and falls to the floor while engaged in some form of physical exertion, as walking about, taking a bath, or straining at stool. Precordial pain, or a tightness through the chest, is often noted; dyspnea is marked, and respiration is rapid and labored, with marked cyanosis. The pulse is rapid and of poor quality, and cold sweat often stands out on the face, which bears an anxious expression. The extremities are cold and clammy, and death often follows within five to twenty minutes. The presence of noticeable varicose veins, or previous thrombophlebitis, lends much weight to the diagnosis of pulmonary embolism.

Since very little can be done in the treatment of pulmonary embolism, once the condition has developed, precautionary measures are necessary in surgery of the abdomen and pelvis where one is working in close proximity to the large iliac vessels and their tributaries. Patients with varicose veins and those with foci of infection, with organisms entering the blood stream from time to time, are more susceptible than others. Anesthesia should be as short as possible, and in patients with weak heart action digitalis previous to operation is advisable. Most authorities agree that lying long in any position without moving tends to the formation of thrombosis.

PULMONARY FAT EMBOLISM*

GEORGE E. SUTTON

Pulmonary fat embolism has been most often noted in cases of fractured bones.[1] It has long been known that free liquid fat is present in the blood following injury to fatty tissue, and emboli in other organs have been observed. Just why the bulk of fat, when placed in the blood stream, should lodge in the lungs is a matter of speculation. Gauss has shown that by the simple addition of oil to blood the viscosity is greatly increased, thereby slowing the stream as it passes through the lung capillaries which are long and poorly supported.

It has been shown that pulmonary fat embolism is at least a potential factor in the cause of death following any surgical operation in which fatty tissue has been injured. The condition has occurred following any type of operation in the abdomen through the abdominal wall, following removal of the mammary glands both radical and simple, herniotomy, inguinal and ventral, removal of fatty tumors, thyroidectomy, and injury to bony tissue, especially by fracture. Warthin also found it following burns.

ETIOLOGY

Man normally has from 0.5 to 0.85 per cent of fat in the blood. The amount may be increased somewhat by ingestion. In certain diseases, such as diabetes mellitus, nephritis, tuberculosis, malaria, and cholera, and also following poisoning by phosphorus and carbon monoxid, the fat content of the blood is increased. In order to permit the entrance of fat into the circulation in amounts even to approach the amount of free fat in the blood stream in pulmonary fat embolism, there must first be injury to the fatty tissue, and second a break in the continuity of the blood stream. Entrance of fat into the circulation by way of the lymphatics is lightly regarded.[1] If the vascular system is injured sufficiently to take up fat, there are several factors which make it easy literally to fill the blood stream with free liquid fat. Partial hemostasis is particularly important. Other factors are mobility of the injured parts, weakened circulation, incomplete or shallow breathing, and inhalation of lipoidal solvents. Bissell believes that certain fats, from the gross appearance, are probably more readily taken up by the blood than others.

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* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, 1921. From the Section on Pathologic Anatomy, Mayo Clinic. Reprinted from Annals of Surgery, 1922, lxxv, 581–590.

That incomplete hemostasis is an important factor is shown by the fatal cases after operations have been performed on the abdominal wall. Almost without exception hematomas filled with fat droplets have been found at necropsy. The same may be said of operations on the breast which have had a fatal outcome from pulmonary fat embolism.

I believe that mobility of the injured tissue is probably the most important factor in the etiology, if there is injury to the fatty tissue and a break in the venous or capillary circulation. In the abdominal wall and in the chest wall mobility depends on the rate of respiration. There are generally at least eighteen complete excursions each minute, and these may be increased to forty or more. If excavation is performed, and it usually is, this, by a vacuum effect, causes free fat to be forced into the opened blood stream. Then, negatively speaking, in the Kondoleon operation in which a large amount of fatty tissue is destroyed, no deaths from pulmonary fat embolism have been reported. The limb, following operation in these cases, is firmly bandaged and kept at rest for at least a week. It was a common observation during the war that many of the wounded, especially those with fractures, who were transported great distances before proper surgical measures could be taken, suffered from pulmonary fat embolism. I noticed this complication particularly in one location. In the exigency of war two armies were placed side by side. The ambulance corps was just behind, drawing wounded from each. One army had ample splints to use, the other had none. Almost without exception the patients with non-splinted fractures of large bones were found in very poor condition. The ordinary resuscitation methods aided these patients but little, and even in cases with poorly splinted fractures the mortality was high. I performed necropsies in eight fatal fracture cases and found an astonishing amount of fat in the lungs in all.

The entrance of fat into the previously weakened circulation tends further to weaken it. When fat enters the venous circulation the venous pressure is increased and the arterial pressure decreased, consequently the blood flows at a slower rate. As has been shown by various writers[1, 12] when free liquid fat enters the venous circulation, most of it collects in the pulmonary capillaries. If there is incomplete aëration of the lung by shallow respiration, the free liquid fat tends to remain there and more collects as it enters the pulmonary circulation.

SYMPTOMS

There are two types of symptoms, pulmonary and cerebral. They may appear singly or in combination. In the pulmonary type the respiratory rate is increased and shallow; dyspnea soon develops, followed by cough and cyanosis; expectoration may be present and there may be blood in the sputum. The pulse rate is increased and the pressure is low. The radial pulse is very small in a great many cases. These symptoms may come on exceedingly fast. In one case reported by Bissell the respiratory symptoms began to appear during operation. The amount of liquid fat liberated into the blood stream seems to determine the suddenness of symptoms. There is a type of case in which the symptoms are dormant or absent for a time; later the respiratory symptoms appear. These may appear, then partly or wholly disappear, and reappear again in from five to twelve days with fatal result.[1] This is explained as being due to fat passing through the pulmonary circulation into the general circulation and again collecting in the pulmonary capillaries. The temperature is of two types: In a case confounded with shock the temperature is normal or subnormal, and the skin and mucous membrane are blanched or ashen. In the majority of cases the temperature is elevated; in fact, it is quite the exception to have a normal or subnormal temperature. In only two of the fatal cases in the Mayo Clinic since 1916 has the temperature been normal. Often there is a sudden elevation of temperature before death. If there is bloody expectoration it is explained by the rupture of some of the capillaries of the lung. This produces hemorrhages into the bronchial tree, which are similar to the patches on the surface of the lung in the form of small petechial hemorrhages.

When the fat passes through the pulmonary system and out into the general circulation the central nervous system may receive an overwhelming amount in the form of emboli. A chain of cerebral symptoms follows, ushered in by restlessness, headache, uneasiness, mental dullness, stupor, and delirium. The delirium may vary from a mild type to a very disturbed state accompanied by hallucination. The reflexes are dulled and tremor, convulsions, and paralysis have been reported. When the cerebral symptoms are predominant the diagnosis is often confounded with delirium tremens. The cerebral symptoms usually appear following the pulmonary symptoms, as a rule, from two to eight days following injury.[1, 4, 7]

Helpful aids to the diagnosis of fat embolism are the discovery of pulmonary edema, on examination of the chest, signs of bronchopneumonia at the bases, the right ventricle dilated, small petechial hemorrhages in the skin over the chest, and blood stained sputum containing numerous fat droplets. Fat droplets appearing early in the sputum is one of the newer signs of pulmonary fat embolism and should not be overlooked. Warthin found them the second day after injury. At necropsy the droplets may be found in the mucous exudate of the trachea and large bronchi. Associated with the fat droplets in the sputum there may be alveolar cells and phagocytes containing fat droplets. Globules of fat may be present in the urine. They are easily detected on the surface if the urine is held up to the light. The lipuria may appear at once; it usually appears at some time during the complication, but death from fat embolism may occur without lipuria. This is explained by retention by the lung tissue of sufficient fat to cause death without free fat being forced into the general circulation. Besides lipuria, there may be casts; certain observers report the presence of brownish casts.[9] In some instances free fat may be obtained from the general circulation by vena puncture.[12] On examination of the eye grounds fat may be seen circulating in the retinal vessels.[3]

In explaining the difference between pulmonary fat embolism and shock many observers assert that there is a quiescent period in pulmonary fat embolism before symptoms appear.[5] This is true in some instances, but in others the symptoms and signs may appear during operation or immediately following injury.

PATHOLOGY

Lipemia, with a subsequent distribution to the tissues, principally the lung, of emboli of liquid fat, is the first pathologic change observed. This takes on the rôle of infarction in the tissues of the body when it leaves the lungs. These infarctions go through the same pathologic change as that of an infarct in the same tissue caused by any foreign material. A wound in the fatty tissue, filled or partly filled with a blood clot and loaded with free fat droplets would seem to be an ideal way of feeding the venous system with fat. If the area is rich in fat, more fat can be distributed to the blood.

The capillaries of the lungs are filled with fat droplets. Fat may be present in the small veins of the tissue of the lung and free fat droplets may be seen in the trachea, large bronchi, and, in some instances, in the smaller bronchi. Often the capillaries of the lungs are ruptured, allowing the escape of the fatty foreign material with localized small areas of hemorrhage. This is particularly noticeable on the surface of the lung where small petechial hemorrhages are seen, which may be red or rusty brown in color, depending on the age of the hemorrhage. The lung shows considerable engorgement of blood. Edema, localized or quite general, is present and usually bronchopneumonia in the lower lobes. When the lung tissue is cut, fat droplets are seen on the blood that runs from the cut surface. The liver, spleen, heart, and adrenals show fatty infarction with fatty degeneration of the tissue involved.[12] Grossly, the kidneys show congestion; staining shows fat emboli in the capillaries. This is partially true of the capillaries of the glomeruli where showers of fat are to be seen. Accompanying the fat in the capillaries of the glomeruli there may be areas of hemorrhage.

INVOLVEMENT OF THE NERVOUS SYSTEM

It is the consensus of opinion that the involvement of the nervous system is a later phase of pulmonary fat embolism[1] There is no particular part of the central nervous system where fat emboli have not been found. Fat is present in the retinal vessels, in the capillaries of the grey and white matter, and in the capillaries of the cord. It is often seen in the perivascular spaces of the vessels in the central nervous system. Edema of the nerve tissue adjacent to the emboli often occurs.

Wilms believes that a considerable quantity of fat in the blood stream, which subsequently lodges in the lungs and other organs, comes by way of the lymphatics. On this theory he inaugurated treatment by drainage of the thoracic duct in case of pulmonary fat embolism. The lymphatic system plays a part in the transportation of fat in fat embolism, but it is not the principal channel of transportation. The lymph nodes adjacent to a wound causing pulmonary fat embolism may not show fat. Experimentally the lymphatics of a leg have been removed as completely as possible, and after injury to the leg pulmonary fat embolism occurred.

TREATMENT

If bones are broken or crushed, the member should be kept quiet.[2] If transportation is demanded, the fractured member, if it is an extremity, should be put on an extension splint. The use of an Esmark bandage or a Momberg's belt has been recommended for one-half hour following fractures around the pelvis.[2] Lipoidal solvents in wounds should be avoided. Complete hemostasis is important and in cases in which considerable fatty tissue has been injured, the wound should be drained at its dependent point.

Active treatment has not met with much success. Normal saline injected into the veins has been recommended.[8] Schanz reports good results in the treatment of eight cases by this method. He injects the solution early into several veins, preferably large veins. A 2 per cent solution of sodium carbonate has been recommended by Czerny; Minich believes this to be useless. Experimentally it does relieve the dyspnea. Wilms recommends drainage of the thoracic duct and reports success by this treatment in one case.

Because of the extra strain placed on the right side of the heart by the increased resistance in the pulmonary circulation, one should use intravenous medication in small amounts. If large amounts of intravenous solution are to be given either in an attempt to dilute the blood or to "fix" the oil, as in the use of sodium carbonate, it would be better to precede such treatment with venesection. Stimulation and supportive treatment should be undertaken. Cardiac stimulants and heat should be applied to keep the blood flowing at as high a rate as can be maintained.

DISCUSSION

One outstanding point in the analysis of these cases is that an obese person undergoing a major operation, particularly if it is necessary to destroy fatty tissue, undergoes an added risk. In the greater number of cases the symptoms appear suddenly; they may develop even during the operation. A point of differentiation that has been made between shock and pulmonary fat embolism is that the symptoms of pulmonary fat embolism make their appearance later. This, as shown by the Mayo Clinic series, is not necessarily true.

Death from pulmonary fat embolism is relatively rapid. Most of

Note.—The thesis as submitted contained detailed illustrated reports of sixteen cases ncluding temperature charts. The cases are summarized in the accompanying table.

TABLE I

Analysis of Cases in Which Death Occurred from Pulmonary Fat Embolism*

Case.	Operation of injury.	Age, years.	Weight, pounds.	Height.		Temperature, degrees.	Pulse.	Onset of symptoms.	Time until death.	Clinical diagnosis.	Distribution of fat (at necropsy).
				Feet.	Inches.						
A176353	Multiple fractures.	75						At once.	2 hours.	Shock.	Lungs, right side of heart, and inferior vena cava.
A176352	Multiple fractures	44						At once.	1 day.	Shock.	Lungs, pulmonary artery, and inferior vena cava.
A179570	Multiple fractures.	28				99	140	1 day.	3 days.	Shock.	Lungs and inferior vena cava.
A181050	Partial thyroidectomy.	42	278	6	1	99–101.5	80–100	At once.	6 days.	Cardiac dilation.	Lungs.
A186135	Laminectomy.	31	142	5	6	103.8	135	1 day.	2 days.	Meningitis.	Lungs.
A185831	Inguinal hernia.		175	5	3	103.5	100–140	At once.	1 day.	Intestinal obstruction.	Lungs.
A191362	Ventral hernia.	67	160	5	8	100–102	80–120	2 days.	11 days.	Pneumonia.	Lungs.
A192661	Umbilical hernia.	53	225	5	3	100–101	100–130	2 days.	6 days.	Pulmonary fat embolism.	Lungs, inferior vena cava, and aorta.
A193911	Cholecystectomy.		Obese.				130		15 hours.		Lungs.
A212639	Fracture.	9				102	120	At once.	8 hours.	Shock.	Lungs.
A202195	Total abdominal hysterectomy.	50	147	5	3	105	100	At once.	20 hours.	Shock.	Lungs, mucus of trachea, and bronchi.
A202891	Total abdominal hysterectomy.	52	200	5	7	103.8	120	8 hours.	5 days.		Lungs, inferior vena cava, and portal vein.
A108053	Ventral hernia.					99–100	99–126	12 hours.	2 days.	Pulmonary fat embolism.	Lungs, mucus of trachea, and bronchi.
A268997	Tumor of the thigh.	59				101–102	100–120	12 hours.	3 days.	Pulmonary fat embolism.	Lungs.
A265230	Cholecystectomy.	59	160			98.5	90–120	During operation.	12 hours.	Cardiac insufficiency.	Lungs, right side of heart, pulmonary artery.
A168252	Postoperative ventral hernia.	60	229			99–100	130	8 hours.	3 days.	Pulmonary fat embolism.	Lungs.

* These cases date from the year 1916, and do not include the three cases reported by Bissell in 1917.

the patients in the series died on the first, second, or third day after operation. Only one patient lived eleven days; one lived six days.

A positive diagnosis was made in four cases. In one (Case A202195) the surgeon inserted a glass tube with gauze into the wound hoping to prevent the absorption of fat. The patient died in twenty hours of pulmonary fat embolism.

The temperature was elevated in all cases.

All of the cases in the series, and the three reported by Bissell were proved by necropsy. Necropsy was not permitted in two other cases in which all the clinical symptoms pointed to pulmonary fat embolism.

Stimulative treatment and normal saline intravenously seemed to have little effect.

Pulmonary fat embolism should be taken into consideration as a complication in any surgical case in which there is destruction of fatty tissue and in which there are symptoms of cyanosis, rapid or labored respiration with or without cough, elevated temperature, and an increased pulse with a low tension. The sputum, urine, and the eye grounds should be investigated for fat.

ILLUSTRATIVE CASES

Abstracts of cases are presented in order to show that postoperative lipemia and pulmonary fat embolism are frequently postoperative complications, and that they are not caused by a mass of fat in the heart or its adjacent large blood vessels, as is generally believed.

Case 1 (A176353). A man, aged seventy-five years, was brought to the hospital *in extremis* after being transported thirty-five miles by rail from the scene of a railroad accident. Death occurred two hours later.

Necropsy revealed, besides multiple fractures of the bones of the body, a large amount of liquid fat in the inferior vena cava, the right auricle and ventricle, the pulmonary artery, and the lung parenchyma (Fig. 174).

Case 2 (A179570). A man, aged twenty-eight years, was operated on for compound fracture of both femurs and the left humerus. Death occurred on the third day.

Necropsy revealed fat droplets running from the cut surface of the lung and in the blood of the inferior vena cava (Fig. 175).

Case 3 (A181050). A man, aged forty-two years and weighing 278 pounds, had multiple adenomas of the thyroid. Thyroidectomy was performed. Convalescence was uneventful until the third day, when the patient became mentally disturbed and later delirious. Death occurred on the sixth day.

Necropsy revealed a few petechial hemorrhages over the visceral pleura and an unusual amount of blood containing free fat droplets in the lung parenchyma (Fig. 176).

Case 4 (A185831). A man, aged thirty-one years and weighing 175 pounds, was operated on for left inguinal hernia. Seventeen days later symptoms of obstruction made a second operation necessary, at which a piece of scarred omentum causing obstruction was removed. Death occurred twenty-four hours later.

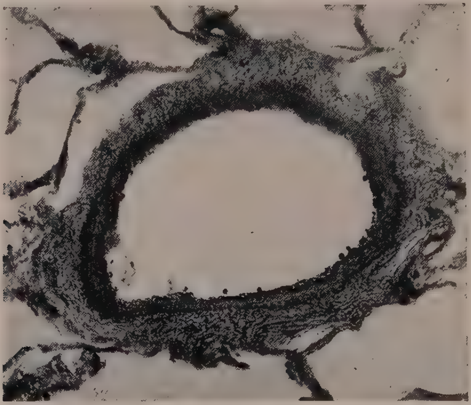

FIG. 174 (Case A176353).—Section through a large vessel showing small fat droplets. From the size of the vessel this is probably the amount of fat that is free in the bloodstream. (×50.)

Necropsy revealed patches of semiconsolidation in the lower lobe of the right lung, intermingled with edema and large amounts of free fat in large and small globules in the blood of the cut surface of the lung (Fig. 177).

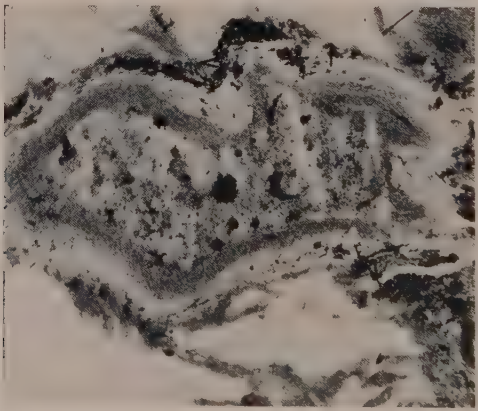

FIG. 175 (Case A179570).—Exudate from a bronchus containing fat. (×50.)

Case 5 (A191362). A man, aged sixty-seven years, weighing 160 pounds, was operated on for postoperative ventral hernia. The hernia was repaired by a plastic operation and a spermatocele was removed. The symptoms began to appear on the second day with slightly increased temperature and pulse. Moderate cough and a slight amount of bloody sputum were accompanying symptoms on the fourth day. The sputum was negative for tuberculosis bacilli. Death occurred on the eleventh day.

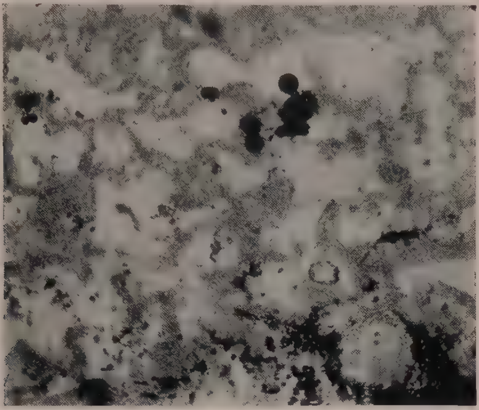

Fig. 176 (Case A181050).—Showers of small fat droplets filling the capillaries of the lung. The larger vessels are quite filled with fat. (×50.)

Necropsy revealed pulmonary fat embolism, petechial hemorrhages over the visceral pleura, edema of the lungs, obliterative fibrous pericarditis, and a large hematoma in the operative wound (Fig. 178).

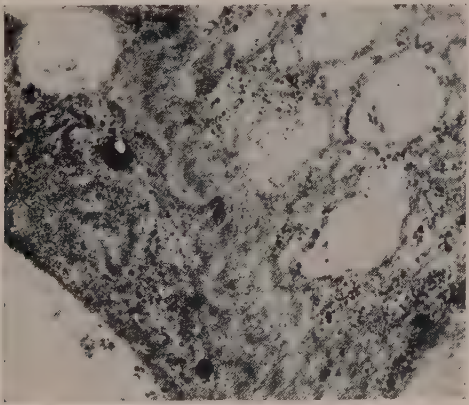

Fig. 177 (Case A185831).—Showers of fat droplets in capillaries and larger vessels of lung and numerous fat droplets in alveoli. (×50.)

Case 6 (A192661). A woman, aged fifty-two years, weighing 225 pounds, was operated on for incarcerated umbilical hernia, at which the adherent omentum was separated and a segment of omentum removed. Two days after operation the temperature rose; the pulse remained between 120 and 130 for five days, then increased to 140 on the sixth day when death occurred.

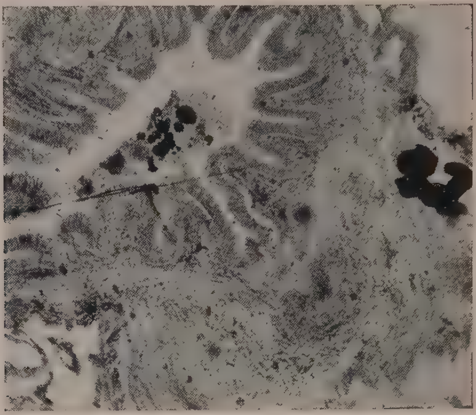

Fig. 178 (Case A191362).—Large vessels and capillaries contain fat. Fat droplets are also in the exudate of the bronchus. (×50.)

Necropsy revealed fat droplets in the blood of the aorta and the inferior vena cava. The lungs were hyperemic and fat droplets were present in the blood from the cut surface (Fig. 179).

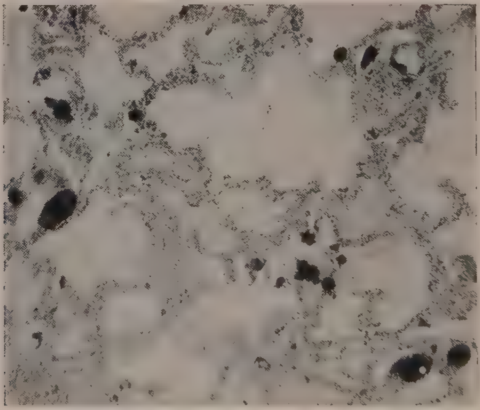

Fig. 179 (Case A192661).—Capillaries and larger vessels filled with fat. (×50.)

Case 7 (A212639). A boy, aged nine years, was operated on for fracture of the lower end of the right femur with sequestrum. The end of the femur protruded through the scar of the former operation and was necrotic. The granulation tissue was curetted, the skin edges removed for 0.6 cm. around the old infected scar, the ends of bone were freshened and the epiphysis replaced and held by two nails. The wound was left open. Death occurred eight hours later.

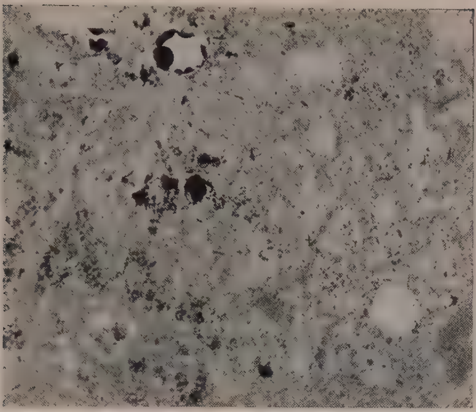

FIG. 180 (Case A212639).—Showers of small fat droplets in the lung capillaries and mucous exudate of alveoli. The large sized vessels are filled with fat. (×50.)

Necropsy revealed large globules of fat in the vessels of the lungs and smaller ones throughout the parenchyma (Fig. 180).

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A STUDY OF THE S-T INTERVAL IN ONE THOUSAND TWENTY-EIGHT ELECTROCARDIOGRAMS*

J. ARTHUR BUCHANAN

One thousand twenty-eight electrocardiograms from 924 patients, made in the Mayo Clinic from January 1, 1918 to June 1, 1918, were studied in order to determine the frequency and associations of variations in the length of the S-T interval. The results of the investigations are as follows:

The normal S-T interval is estimated at 0.28 seconds.

Sinus rhythm in normal hearts.—Sixty-nine of these electrocardiograms showed an average length of 0.28 seconds in all three derivations. Nine showed prolonged S-T intervals, from 0.29 to 0.34 seconds in any derivation, with an average of 0.31 seconds. Two showed a shortened S-T interval, with an average of 0.20 seconds.

Sinus tachycardia.—One hundred forty-eight electrocardiograms were made from normal rapid hearts: The average S-T interval was 0.24 seconds. Six showed a prolonged interval averaging 0.31 seconds. Twenty-nine showed a shortened interval varying from 0.16 to 0.22 seconds, with an average of 0.19 seconds.

Sinus rhythm in abnormal hearts.—The average S-T interval for the group of 143 electrocardiograms was 0.30 seconds, a slight prolongation of the time interval for the whole series. Thirty-one showed a prolonged time interval; three cases showed a shortened interval.

Sinus tachycardia in abnormal hearts.—One hundred thirty-two cases showed an average S-T interval of 0.22 seconds; four electrocardiograms showed a prolonged interval. A shortened interval was found in twenty-nine.

Premature ventricular contractions.—In one hundred forty-three electrocardiograms the average S-T interval was 0.38 seconds. Prolongation occurred in twelve cases, and shortening appeared in three.

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* Abstract of paper published in full in the Archives of Internal Medicine, 1921, xxviii, 484–494. From the Section on Medicine, Mayo Clinic.

Premature auricular contractions.—Fifty-five electrocardiograms were studied and the average S-T interval was 0.27 seconds. Eleven electrocardiograms had a prolonged S-T interval. Shortening was observed in one electrocardiogram.

Sinus bradycardia in the normal heart.—Forty-eight electrocardiograms showed a ventricular beat of less than 70 each minute. The average S-T interval for this group was 0.33 seconds, twenty-three of the electrocardiograms showing a prolonged S-T interval. A shortened interval did not occur in this group.

Sinus arrhythmia in the normal heart.—This condition was found in twenty electrocardiograms. The average S-T interval was 0.29 seconds. A prolonged interval occurred in nine electrocardiograms, and a shortened interval was not observed.

Sinus arrhythmia in the abnormal heart.—Fifteen electrocardiograms in this group showed an average S-T interval of 0.28 seconds. A prolonged interval was found in eight, and a shortened one in two electrocardiograms.

Auricular fibrillation.—In eighty-one electrocardiograms the average S-T interval was 0.22 seconds. A prolonged interval was observed in three instances, and a shortened interval in thirty-three instances.

Left ventricular preponderance.—This was observed in 434 electrocardiograms. The average S-T interval was 0.26 seconds. Ninety-seven showed a prolonged interval, and thirty-five a shortened interval.

Right ventricular preponderance.—In 166 electrocardiograms in this group, the average S-T interval was 0.25 seconds. In twenty-two instances there was a prolonged S-T interval, and in thirty-three a shortened interval.

Angina pectoris.—Electrocardiograms were made from twenty-seven patients with angina pectoris. The average S-T interval was 0.26 seconds. Three patients showed a prolonged interval. In two patients the interval was shortened. There was no change in the S-T interval after exercise.

Aberrant Q R S complexes in all derivations.—Sixty electrocardiograms in this group showed an average S-T interval of 0.20 seconds. A prolonged interval was found in four, and a shortened interval in twelve instances.

Partial or complete heart block.—Five cases showed an average S-T interval of 0.27 seconds. The interval was prolonged in two cases and shortened in one case.

TABLE 1.—Comparative Frequency of Prolonged S-T Interval

Cases	Normal hearts	Percentage prolonged
23	Sinus bradycardia	47
9	Sinus rhythm	13
9	Sinus arrhythmia	4
6	Sinus tachycardia	4
	Abnormal hearts	
40	Sinus bradycardia	72
8	Sinus arrhythmia	53
2	Heart block	40
97	Left ventricular preponderance	22
31	Sinus rhythm	21
11	Auricular extrasystoles	20
22	Right ventricular preponderance	13
12	Ventricular extrasystoles	8
4	Aberrant Q R S Complexes	6
4	Sinus tachycardia	3
3	Auricular fibrillation	

TABLE 2.—Comparative Frequency of Shortened S-T Interval

Cases	Normal hearts	Percentage prolonged
29	Sinus tachycardia	19
2	Sinus rhythm	2
0	Sinus bradycardia	0
0	Sinus arrhythmia	0
	Abnormal hearts	
33	Auricular fibrillation	40
29	Sinus tachycardia	21
1	Partial heart block	20
12	Aberrant Q R S complexes	20
33	Right ventricular prepondorance	19
2	Sinus arrhythmia	13
35	Left ventricular preponderance	8
3	Ventricular extrasystoles	2
3	Sinus rhythm	2
1	Auricular extrasystoles	0.9
0	Sinus bradycardia	0

Sex and age.—Of the 287 electrocardiograms showing a prolonged S-T interval, 60.97 per cent were made from males. Of the 185 electrocardiograms showing a shortened S-T interval, 60 per cent were made from females. This is due to the greater frequency of exophthalmic goiter in females.

Blood pressure.—The unimportance of blood pressure in variations of the length of the S-T interval is shown in Table 4.

T wave negativity.—This phenomenon was observed in 511 electrocardiograms. The S-T interval was prolonged in Derivation I with T wave negativity in six patients, and in forty-two patients in Derivation III. In combination the S-T interval was found prolonged in

TABLE 3

Age of Patients, in Decades, Manifesting Change in S-T Interval

	Patients with prolonged S-T interval.	Patients with shortened S-T interval.
0 to 10	0	9
11 to 20	10	9
21 to 30	27	37
31 to 40	64	37
41 to 50	63	43
51 to 60	64	31
61 to 70	50	17
71 to 80	9	2

TABLE 4

Relation of Blood Pressure to S-T Interval

	Normal hearts.		Abnormal hearts.		Normal hearts.				Abnormal hearts			
					Prolonged S-T interval.		Shortened S-T interval.		Prolonged S-T interval.		Shortened S-T interval.	
	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.	Systolic.	Diastolic.
Sinus rhythm	128	79	148	77	133	80	130	76	140	80	163	49
Sinus tachycardia	140	73	132	68	151	85	153	86	134	85	141	65
Sinus bradycardia	123	72	135	78	127	77			146	77		
Sinus arhythmia	113	73	128	73	117	70			135	72	125	81
Auricular fibrillation			144	63					133	63	130	79
Left ventricular preponderance			145	81					144	84	140	75
Right ventricular preponderance			126	74					132	78	197	161
Angina pectoris			151	88					148	103	160	80
Aberrant Q R S complex			152	86					147	86	162	75

association with T wave negativity once in Derivations I and II, twice in Derivations I, II, and III, and three times in Derivations II and III. The S-T interval was shortened in Derivation I three times in association with T wave negativity, and twenty-two times in Derivation III. The interval was found shortened with T wave negativity in combined Derivations I and II, six times; in Derivations I, II, and III, six times, and in Derivations II and III, six times.

Exophthalmic goiter.—Electrocardiograms were made from eighty-one patients. Forty-two showed a normal S-T interval, three a prolonged interval, thirty-three a shortened interval, and in three the interval was obscured by auricular fibrillation. The frequency of shortened S-T interval in exophthalmic goiter is sharply contrasted with the infrequency of this finding in cases of adenoma with hyperthyroidism. In thirty-seven electrocardiograms made from cases in the latter group, the S-T interval was shortened seven times, and prolonged six times.

DISCUSSION

Variations in the length of the S-T interval are common. Of the 1,028 electrocardiograms studied a total of 472 (44 per cent) showed an abnormal length of the interval. Prolongation (27 per cent) is more frequently observed than shortening (18 per cent). The data presented demonstrate the lack of a constant relationship of variation in the length of the interval with any other phenomena in the electrocardiogram. It is to be noted, however, that prolongation is found more often in slow hearts, while shortening is found more often in rapid hearts. There is an intimate relationship between cardiac rate and length of the S-T interval.

A study of the clinical diagnosis clearly shows that there is no organic lesion of the cardiac structures which is constantly associated with a variation in the length of the S-T interval.

It might be suspected that interference with the conduction apparatus would have a constant bearing on the length of the S-T interval. This does not hold true.

It is safe to believe that no anatomic condition of the heart can cause, by itself, variation in the length of the S-T interval.

CONCLUSIONS

1. The normal time period of the S-T interval ranges from 0.24 second to 0.28 second.
2. Variations in the length of the S-T interval are common.
3. Variations are independent of anatomic lesions.
4. The length of the S-T interval is more dependent on cardiac rate than any other factor.
5. Variations in the length of the S-T interval are not a constant accompaniment of any of the other phenomena of the electrocardiograms.
6. Males present variations in the length of the S-T interval slightly more often than females.
7. Variations in the length of the S-T interval are suggestive of retardation or acceleration of the rate of change in electropotential.

V

SKIN AND SYPHILIS

MALIGNANT ENDOTHELIOMAS AS EXEMPLIFIED BY THREE CASES WITH CUTANEOUS INVOLVEMENT*

GEORGE J. BUSMAN

Three cases of tumors whose cellular elements present the histologic characteristics of endothelial cells are reported.

The clinical course of the lesions in general is that of tumors of slow growth often developing at sites of trauma. Metastasis does not appear until late, when the tumor has reached considerable size. The tumors in all cases exhibit a marked hemorrhagic tendency (Figs. 181 and 182).

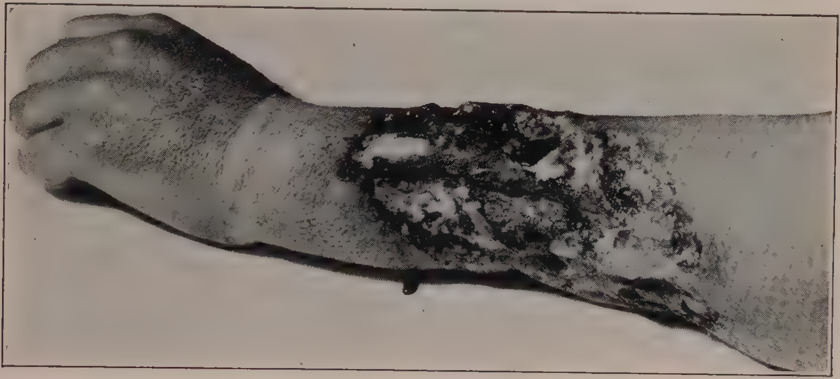

Fig. 181.—Forearm of patient showing the large ulcer.

Clinically, the lesions must be distinguished from syphilis, carcinoma, sarcoma, sporotrichosis and the infectious granulomas. The hemorrhagic character of the tumor, the relatively benign course of the lesion, the long delayed metastasis, and the good general condition of the patient are features which should lead one to suspect malignant endothelial tumor. A final diagnosis, however, is practically impossible without histopathologic study.

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Dermatology, 1922. Published in the Archives of Dermatology and Syphilology, 1922, 680–700. From the Section on Dermatology and Syphilology, Mayo Clinic.

Because of the variability in arrangement of endothelial cells, the ability of the cells to undergo metaplasia, the distortion of the original picture by secondary factors, such as infection and the difficulty of tracing the tumor cells through their transition stages to pre-existing endothelium, the earliest lesions obtainable should be employed in the histopathologic study.

The histologic structure of the tumors is that of an undifferentiated polymorphic-celled type of growth presenting a whorled arrangement of the cells with the formation of elongated strands and narrow trabeculæ. There is definite evidence of an attempt to differentiate into vascular structures. A constant feature is the occurrence of vacuoles in the cytoplasm of practically all cells. These vacuoles coalesce, with the resultant formation of large spaces. The cells bordering on these spaces arrange themselves in rows, become elongated, and form an endothelial lining of the space. There is a close association of the tumor with blood vessels. Capillary and sinus-like channels are formed which may contain blood, but have no apparent connection with the circulation of the host.

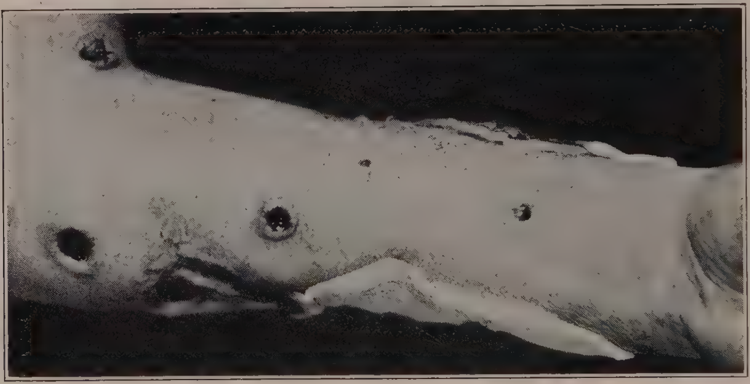

Fig. 182.—The under surface of the forearm of patient in Figure 181, showing new nodules which developed and broke down while the patient was under observation.

According to the interpretation which is placed on the morphology and histogenesis of the endothelial cell, the tumor may be regarded either as a structure of mesoblastic or connective tissue origin, histogenetically a sarcoma, or it may be regarded as a tumor composed of cells resembling epithelium, and hence, morphologically, carcinoma (Figs. 183 and 184).

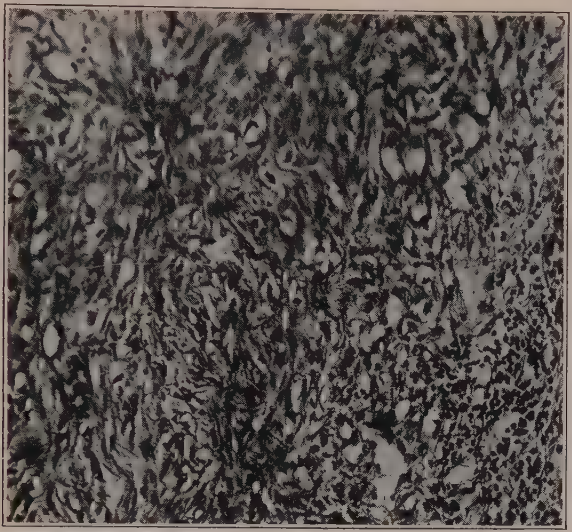

FIG. 183.—Denser part of the tumor in patient in Figure 181, showing early stages of vacuole formation. (×160.)

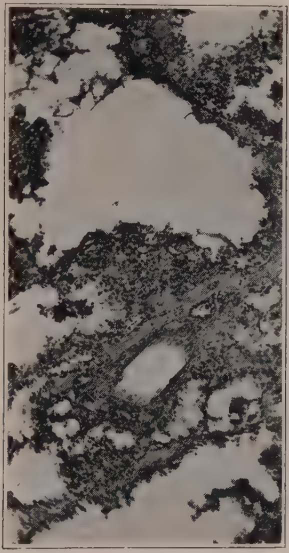

FIG. 184.—Cavernous structure characteristic of the tumor in the third patient. (×50.)

The term "endothelioma," as applied to the cases described, must stand essentially as a name representing a compromise between the histogenetic and the morphologic views of the classification of tumors.

Treatment consists of radical surgical removal of the original process followed by roentgen-ray or radium applications to the site of the original lesion and all probable areas of metastasis.

A gradual change in current opinion and a decline in the opposition to the conception of endotheliomas as a type of neoplasm has occurred during the past five years. The three cases described help to substantiate the belief that malignant endothelioma is an actual pathologic entity.

A REPORT OF FIVE CASES OF SO-CALLED ACRODYNIA*

MORLEY D. McNEAL

Five cases presenting the syndrome first described by Weston as acrodynia are described. The outstanding features were the cutaneous and nervous system manifestations and marked loss in weight. The muscles of the patients were soft and flabby, and weakness was so marked that standing without support was impossible. Some of the children beat their heads against the floor, some bit their fingers and rubbed them against their teeth so that the fingers and hands became macerated and infected.

A fairly profuse papular eruption was present over the trunk and extremities in all cases. The lesions were of pin-point size and a light red color, occurring usually in closely studded patches. A variable amount of swelling was present in the fingers and great toes, but the extreme erythema, swelling, and cyanosis reported by other observers were not noted. Redness of the oral mucous membranes was present in all cases and in three there were oral infections.

While the term "acrodynia" may hardly be justifiably used to describe these cases, there are sufficient points of resemblance between them and the cases described by other authors to admit of their grouping in the same category.

The details of the histories of the five cases are presented.

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* Abstract of paper published in full in Minnesota Medicine, 1922, vi, 153–156. From the Section on Pediatrics, Mayo Clinic.

A HYALOMA (PSEUDOCOLLOID MILIUM OR COLLOIDOMA ULCEROSUM?) SIMULATING MORPHEIFORM EPITHELIOMA: REPORT OF A CASE*

RUDOLPH RUEDEMANN, Jr.

The author reports a case of hyaloma with the clinical and histopathologic picture. The lesion simulated in a great many respects what is commonly known as colloid milium, although the clinical picture and

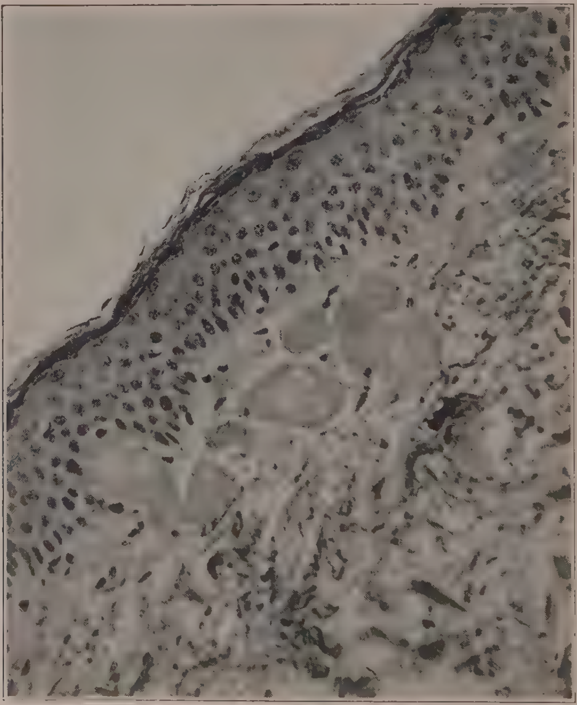

Fig. 185.—Group of hyaline bodies in the apex of a papilla.

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* Abstract of paper published in full in the Archives of Dermatology and Syphilology, 1922, v, 591–596. From the Section on Dermatology and Syphilology, Mayo Clinic.

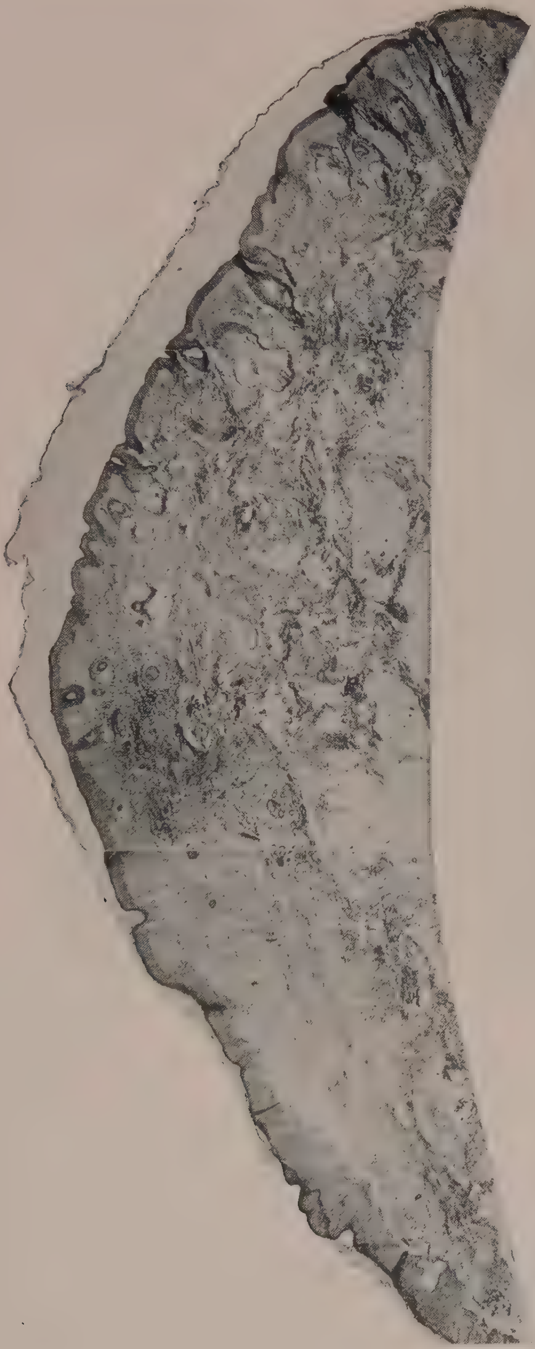

Fig. 186.—Section illustrating the transition from inflammatory changes on the left to atrophy on the right. The process is at its height at the center. The hyaline bodies are most numerous in the portion of the section to the right of the center. Hematoxylin-Weigert elastic tissue stain. (×200.)

certain details in the histopathology are unique. The lesion was of four years' duration and occurred in a female thirty-six years of age. The process began as what was described as a small scar on the malar eminence. It had ulcerated repeatedly, healing slowly. At the time of observation the lesion was about 2 cm. in diameter, had a smooth glistening appearance and lardaceous feel. The area was slightly depressed and on palpation showed small subcutaneous nodules. There was some telangiectasis and the border was nodular. Objectively, the lesion suggested a morpheiform epithelioma.

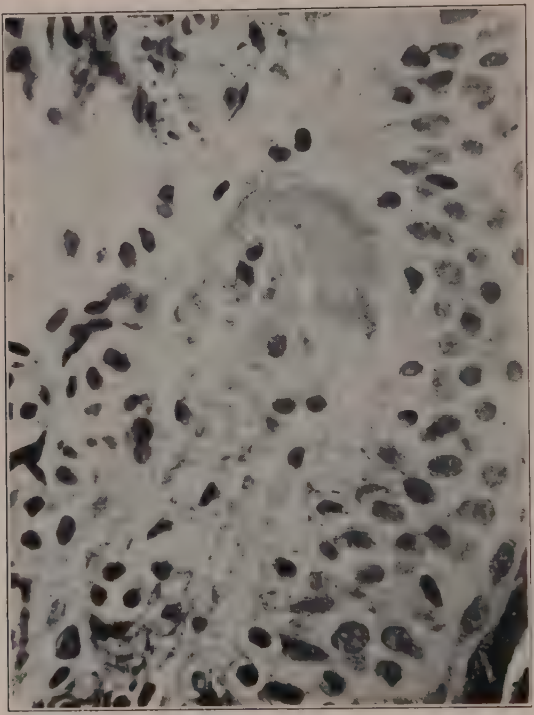

Fig. 187.—Vacuolation and possible invasion of hyaline bodies by macrophages.

Pathologic studies showed that the nodules consisted of clumps of hyaloid material grouped about the papillæ (Fig. 185). The process as a whole was found to be inflammatory. Moderate acanthosis was present, round cell infiltration about the papilla and throughout the corium. New blood vessel formation was present and masses of hyaloid material and connective tissue. The process was most active at the central portion of the lesions, while at the periphery it had subsided

(Fig. 186). The colloid material at the border had largely disappeared and the presence of macrophages in this area suggested that the colloid material had been phagocytized (Fig. 187). There was also atrophy of the corium and thinning of the epidermis in this region.

The picture, in short, was that of a hyaloma apparently resulting from an inflammatory process and leaving behind it atrophy and disappearance of the colloid masses.

T—'22—29

STUDIES OF CEREBROSPINAL FLUID AND BLOOD OF SYPHILITIC AND NORMAL PERSONS WITH SPECIAL REFERENCE TO THE IMMUNITY REACTIONS AND THE COLLOIDAL GOLD TEST ON THE ORIGINAL AND ULTRAFILTERED FLUIDS AND SERUMS*

CHARLES E. NIXON

The investigations reported herewith concern various chemical, physical, and immunologic studies of the cerebrospinal fluid and blood of syphilitic and normal persons, and also the colloidal gold and the Wassermann reactions. The results obtained are as follows:

1. The globulin fraction in the serum of syphilitic persons contains the active substance in the Wassermann reaction. The filtrability of globulin in this serum by the ultrafilter is less than that in the normal serum.

2. Three factors have been considered in this relationship: (a) the possible ease of absorption of the Wassermann reaction active globulin of the ultrafilter, as compared with normal globulin; (b) the possibly greater size of the particle of active globulin, as compared with normal globulin; and (c) the possible instability of the active globulin, as compared with normal globulin.

3. Positive colloidal gold reactions are due to the presence of precipitating substances.

4. Both precipitating and protecting substances are present in pathologic cerebrospinal fluid.

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Nervous and Mental Diseases, 1921. Published in full in the Archives of Internal Medicine, 1922, xxx, 182–215. From the Department of Nervous and Mental Diseases, University of Minnesota, Minneapolis.

5. Curves in Zones I, II and III are due to varying amounts and proportions of the precipitating and protecting substances.

6. Albumin and globulin may possess both precipitating and protecting power.

7. Ultrafiltrates of syphilitic and nonsyphilitic serums give curves that are more or less similar, but there is a tendency to a greater difference between the zones of reduction of the original and filtered serum in the syphilitic than in nonsyphilitic serums.

8. The protecting substance is decreased by ultrafiltration to a greater degree than the precipitating substance.

9. Changes in the state of the protein modifies precipitating and protecting powers.

10. The salt solution used in the colloidal gold test partially neutralizes the protective action.

VI

HEAD, TRUNK, AND EXTREMITIES

OBSERVATIONS ON THE DEVELOPMENTAL ANATOMY OF THE TEMPORAL BONE*

LEE ROGERS

The development of the temporal bone in later fetal life and childhood, and the varying relations of its several parts at different ages, with particular reference to their surgical significance are considered. In the main, study has been limited to those phases of the subject concerning which information is obviously incomplete or concerning which there is a decided difference of opinion.

MATERIAL AND METHODS

A considerable amount of material was available, including 294 temporal bones, some dried, and some fresh and in place, also a series of thirty-two skulls in various stages of development. Of the temporal bones, fourteen were of fetal stages, thirty-two of newborn, eighteen of children of different ages (two to fifteen years, inclusive), and 230 of adults. Of the skulls, fourteen were fetal, fourteen were of newborn, and four were of children. There was also available a large number of adult skulls for comparison with those of earlier stages. The subject has been attacked with a variety of methods.

1. A series of casts was prepared in Wood's metal, reproducing the cavities of the ear. Forty such casts were prepared. Fifteen of these were ears of adults, five of children, ten of newborn infants, and ten of fetuses (Figs. 188–190).

2. The antrums of a series of temporal bones were filled with bismuth paste and roentgenographed to show their position at different ages. As a check on this procedure, the antrums were later transilluminated by introducing the small electric light of a bronchoscope tube in the

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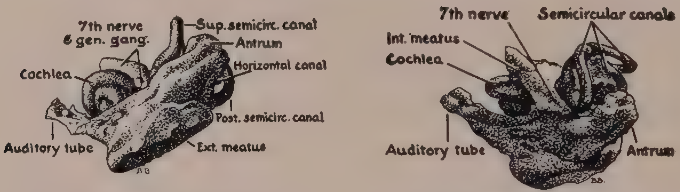
* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science, 1920. Published in full in the Annals of Otology, Rhinology, and Laryngology, 1921, xxx, 103–129. From the Departments of Anatomy and Ophthalmology and Otolaryngology, University of Minnesota, Minneapolis.

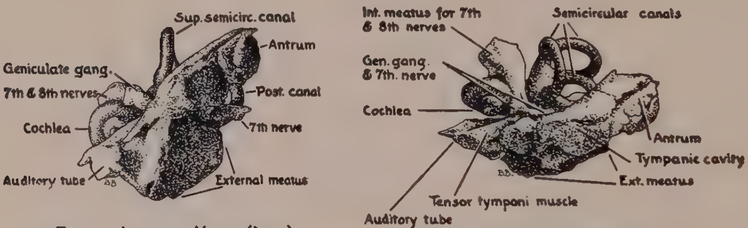
cavity of each bone and tracing the outline on the surface. The size and position of the antrums were thus determined by roentgenography and transillumination in forty instances (ten adults, seven children, eight newborn infants, and fifteen fetuses).

3. In order to determine the relations of the inner structures of the ear to surface landmarks, a series of casts was prepared in Wood's metal



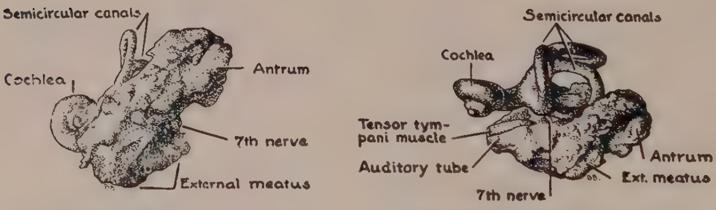
5 MO. FETUS ~ LATERAL VIEW ~ (LEFT)

5 MO. FETUS ~ SUPERIOR VIEW ~ (LEFT)



7 MO. FETUS ~ LATERAL VIEW ~ (LEFT)

7 MO. FETUS ~ SUPERIOR VIEW ~ (LEFT)

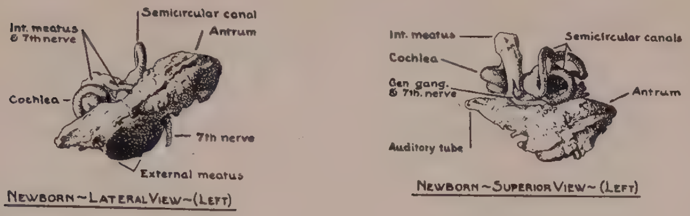


NEWBORN ~ LATERAL VIEW ~ (LEFT)

NEWBORN ~ SUPERIOR VIEW ~ (LEFT)

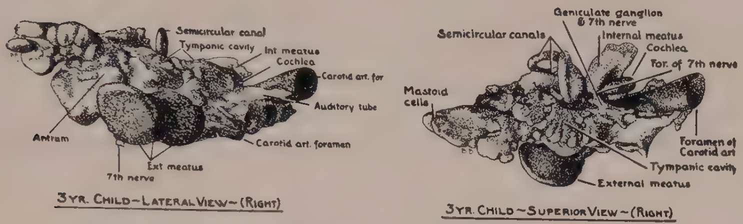
FIG. 188.—Wood's metal casts of internal and middle ear of fetus and newborn; natural size.

and the bone in these specimens was later rendered transparent by the Spalteholz clearing method, so that the cochlea, antrums, nerves, air cells, and so forth, could be observed in situ. Three of these preparations were made, one of an adult, one of a child three years old, and one of a newborn infant.



NEWBORN ~ LATERAL VIEW ~ (LEFT)

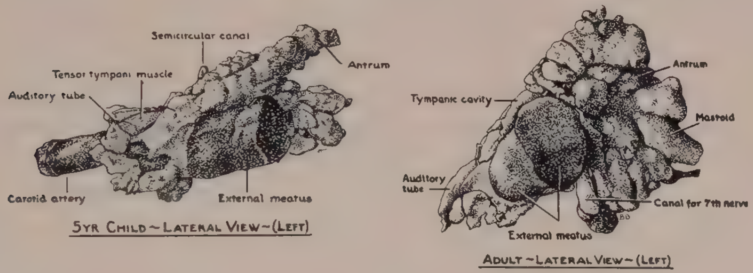
NEWBORN ~ SUPERIOR VIEW ~ (LEFT)



3 YR. CHILD – LATERAL VIEW ~ (RIGHT)

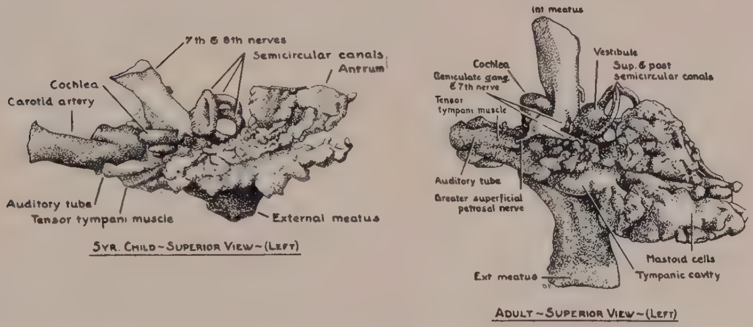
3 YR. CHILD ~ SUPERIOR VIEW ~ (RIGHT)

FIG. 189.—Wood's metal casts of internal and middle ear of newborn and child; natural size.



5 YR CHILD ~ LATERAL VIEW ~ (LEFT)

ADULT ~ LATERAL VIEW ~ (LEFT)



5 YR. CHILD ~ SUPERIOR VIEW ~ (LEFT)

ADULT ~ SUPERIOR VIEW ~ (LEFT)

FIG. 190.—Wood's metal casts of internal and middle ear of child and adult; natural size

4. In order further to determine the relations of the antrums, facial nerve, and other structures to the surface landmarks, regional dissec-

tions were made on the cadaver. Of these eight were of adults, two of children, and eight of newborn infants. The angle of inclination of the tympanic membrane was also determined in fifty-five ear drums in six adults, four children, twenty-four newborn, and twenty-four fetuses.

TECHNIC OF MAKING CASTS OF THE TEMPORAL BONE WITH WOOD'S METAL

The value of the study of the middle and inner ear by means of casts has long been recognized, and in making them a variety of materials have been used to replace the air spaces. Benzold used a mixture of wax and resin, Von Stein used a rubber and chloroform solution, and then vulcanized the mass. Brühl cleared the bone and injected mercury. Brown injected dental rubber and vulcanized. Wood's metal seems to give the most satisfactory results for this type of preparation, and certain refinements of the method introduced here have been found of value.

To make casts of the middle and inner ear, it is best to secure well dried temporal bones in which the nerves and mucous membrane of the cavities have disintegrated and disappeared, so that the canals will be clear. If any of these dessicated tissues remain, they should be removed with the air blast. The canals and nerve openings are then covered with adhesive tape, with the exception of the external auditory meatus, which is left open. After heating the encased bone at about 100 C. for twenty-four hours in a sand bath, it is ready to receive the molten Wood's metal, which is poured into it to the level of the suprameatal (Henle's) spine. As the bone is heated above the melting point of the metal, the latter will not solidify, and the specimen can be agitated to remove air bubbles. It is a good plan to drop a little water on the metal at the meatus to solidify it, and then the bone can be picked up, and rotated to remove the air and get the metal into all parts. After cooling, the plaster of Paris casing is removed and the specimen is placed in 30 per cent hydrochloric acid to dissolve the bone.

TECHNIC OF PREPARING TRANSPARENT BONE SPECIMENS

The method used to render the injected specimens of bone transparent is that developed by Spalteholz in 1906. After the temporal bone is filled with Wood's metal, it is decalcified by placing it in a 2 per cent solution of hydrochloric acid, which is changed daily for one month. It is then transferred to a 1 per cent solution of hydrochloric acid which is also changed daily for two weeks. The bone is washed in running water for two weeks, or until it gives a neutral reaction to blue litmus, after which it is bleached for two hours in hydrogen peroxid. After bleaching the specimen is again washed, then dehydrated by passing it through a series of graded alcohol solutions, 60, 75, 95, and 98 per cent. It should be left in each mixture about twenty-four hours. After dehydration, the specimen is cleared by placing it in benzol for four days, and changing the solution at the end of forty-eight hours. The final preserving fluid in which the specimen is to remain consists of methyl salicylate five parts, and isosafrol three parts. As these fluids have the same refractive index as the prepared bone the latter becomes translucent. Sometimes it may be made more transparent by adding a little more isosafrol. Air bubbles may be removed by placing the specimen under a bell jar and exhausting the air with a suction pump.

THE TYMPANIC MEMBRANE

One is confronted with great variance of opinion in the literature with regard to the inclination of the tympanic membrane. Observers seem to be about equally divided as to whether the inclination in the newborn is equal to, or less than that of the adult, and several maintain that the ear drum is almost horizontal at birth. The data obtained by the measurement of individual ear drums is shown in Table 1. The figures indicate the degree of inclination from the perpendicular. The measurements show that a large individual variation is common in both newborn and adult drums. The averages show that the membrane approaches a little more closely the horizontal fetus and that it gradually becomes more erect in later fetal life. There seems to be no constant change in the angle after birth.

The angles given in Tables 2, 3, and 4 were determined with the stangengoniometer of Martin and Ranke. As these measurements were taken to the extreme edge of the sulcus tympanicus they will be found to be slightly larger than the drum membrane proper.

It is a general statement that the dimensions of the tympanic membranes at birth are almost identical with those of the adult, there being little or no increase in the postnatal period of development. The figures quoted in Table 2 show that the tympanic membrane increases steadily in size in the last half of fetal life and that there is a distinct increase in its diameter in the first year after birth, at the end of which period the adult dimensions are attained. (Tables 1 and 2.)

TABLE 1

Dimensions of the Tympanic Membrane and Ring in Prenatal and Postnatal Life

Age.	Cases.	Average maximal diameter, mm.	Average minimal diameter, mm.
Fetal months:			
Four	2	6.8	5.5
Five	3	7.4	6.2
Six	4	7.6	6.7
Seven	3	8.3	7.7
Eight	3	8.9	7.8
Nine	6	9.3	8.2
Newborn	14	9.8	8.2
Seven months	1	11.0	8.5
One year	1	11.0	9.0
Two years	1	11.0	9.0
Adult	6	11.0	9.0

TABLE 2

The Inclination of the Tympanic Membrane in Prenatal and Postnatal Life

Age.	Cases.	Angle of inclination (degrees).		
		Maximum.	Minimum.	Average.
Fetal months:				
Four	2	63	61	62.0
Five	6	80	55	64.4
Six	6	65	58	61.5
Seven	5	63	55	60.2
Eight	5	65	58	61.4
Nine	8	68	55	60.8
Newborn	9	65	54	57.0
Three years	2	60	55	57.5
Adult	6	69	45	57.5

THE ANTRUM

The relations of the antrum to its adjacent structures vary considerably at different ages. Up to the time of birth the antrum is directly over the meatus, its upper part lying above the zygomatic process and its anterior margin extending forward beyond that of the meatus.

In the fetus and newborn the incus lies in the aditus and its long process projects into the antrum. As the child grows older the antrum gradually shifts from its location above the meatus to a more posterior and inferior position, and in the adult it is directly posterior to it (Figs. 191–193). Its position in the child materially aids drainage in acute infections.

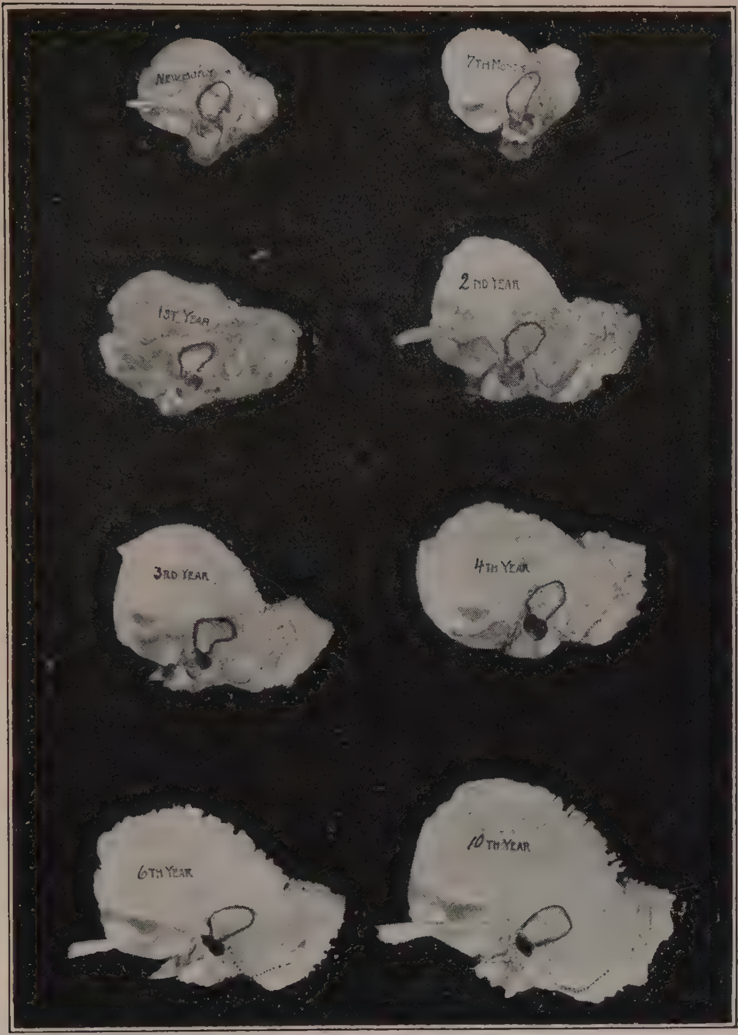


FIG. 191.—A series of temporal bones showing the position of the antrum as determined by X-ray and transillumination.

1. Newborn.
2. Seven months' child.
3. One year old.
4. Two years old.
5. Three years old.
6. Four years old.
7. Five years old.
8. Ten years old.

The lateral (external) canal of the bony labyrinth forms the inner boundary between the antrum and epitympanic recess. Its bony covering is easily recognized as a thin ridge of dense bone. In the

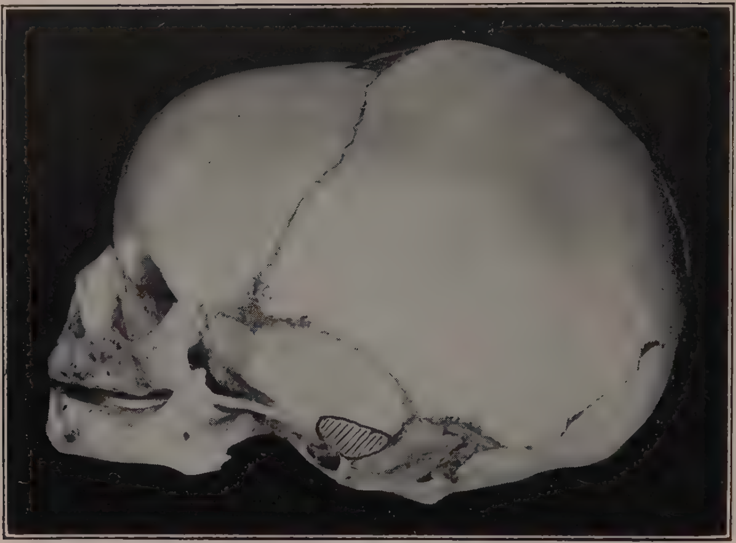


FIG. 192.—Lateral view of skull of newborn child showing position of tympanic antrum as determined by X-ray and transillumination.

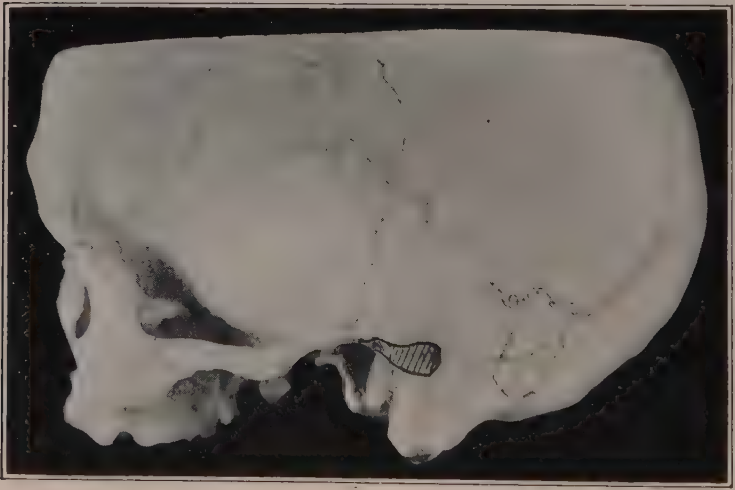


FIG. 193.—Lateral view of adult skull showing position of tympanic antrum as determined by X-ray and transillumination.

young child its wall is only about 0.2 mm. in thickness, and a probe or curette introduced into the middle ear could easily rupture into the canal. The thickness of the bone separating the antrum and lateral canal at different ages is approximately: newborn, 0.2 mm.; child three years old, 0.3 to 0.5 mm.; child five years old, 0.5 mm.; adult, 1 mm.

As the mastoid develops, the antrum becomes farther removed from the external surface of the temporal bone. The thickness of the bony wall bounding the lateral surface of the antrum at different ages is approximately: newborn, 1 to 2 mm.; child five years old, 6 mm.; child ten years old, 10 mm.; adult, 15 mm.

These data are approximately the same as those given by Symington. The dimensions of the antrum in the newborn are about 10 by 11 mm., which is approximately the same as in the adult.

THE FACIAL NERVE

The general course and relations of the facial nerve in the temporal bone are much the same in the infant and adult, and there seems to be a consistent and uniform growth of its parts. The distance from the nerve's entrance into the internal auditory meatus to the central point of the geniculate ganglion is shown in the following: five month fetus, 8 mm.; seven month fetus, 9 mm.; newborn (average of ten cases), 10 mm.; child three years old, 12 mm.; adult (average of ten cases), 13 mm.

The distance from the center of the ganglion to the point where the nerve turns sharply downward is 10 mm. in the newborn, 11 mm. in the child of three years, and an average of 12 mm. in the adult. This portion of the nerve lies within the tympanic cavity, and in its course over the promontory around the fenestra rotundum it is protected only by a thin shell of bone in the adult, and in the child up to the fourth year it is often covered only by a thin membrane of connective tissue. This exposed condition accounts for the liability to facial paralysis in the child following acute otitis media. As the nerve runs directly beneath the anterior part of the external (horizontal) canal, a roughly used probe, or Staeke's director for locating the epitympanic recess may easily injure it. As Cheatle aptly says, "Such an instrument is safe only in experienced hands, and then it is not needed."

The course and relations of the facial nerve can be seen in the superior views of the various casts. The distance from the posterior rim of the tympanic membrane to the nearest point of the facial nerve is from 3 to 5 mm., in the fetus and in the adult.

The exposed condition of the nerve, in early life, after its exit from the stylomastoid foramen, is of importance both to the obstetrician and the surgeon. In the fetus and young infant it emerges about 3 mm.

behind and a little below the most posterior part of the margin of the tympanic membrane. As there is no mastoid process at this time, the nerve runs downward over the petrous portion of the bone. This condition accounts for some of the facial paralyses produced by pressure with instruments at this point during delivery. It is also to be noted that this external portion of the nerve lies in the path of an incision such as is made in operation for mastoiditis in the adult. If such an incision were made in the infant, the nerve would be cut and facial paralysis would result; but as the antrum in the young child is much higher and as there is no mastoid containing air cells, there is little need for such an incision. The relations of the exit of the facial nerve, the antrum, the tympanic membrane, and the developing mastoid process are shown in Figures 191 to 193.

After the first year the vertical portion of the facial nerve is gradually covered by the deposit of the layers of bone forming the mastoid process, and by the outward growth of the posterior portion of the tympanic ring, which forms the osseous meatus. The thickness of the bone over this portion of the nerve is shown by the following measurements: child one year, 0 mm.; child three years, 6 to 10 mm.; child five years, 11 mm.; adult, 13 to 15 mm.

In all fetal and infant specimens examined the nerve came straight to the surface, but, as Freligh says, in some cases the nerve bends downward before emerging, and in these cases the exit would be 2 or 3 mm. lower.

THE INNER EAR

If lines were projected through each posterior canal, they would meet a little posterior to the hypophysis and form approximately a right angle. Likewise, lines through the superior semicircular canals would meet above the posterior rim of the foramen magnum and be approximately at right angles to each other. It can be seen that the canals of one side are at right angles, and that either canal of one side is at right angles to its mate on the other side. This makes the posterior canal of one side parallel to the superior canal of the other and vice versa. On measurement it is found that in only about 33 per cent of the cases are these angles exactly 90 degrees. Other cases will vary 10 degrees above or below.

Lines projected through the superior canal of the newborn meet within the foramen magnum, while in the adult they meet well back of it. This is partly due to the fact that the foramen magnum is more posteriorly located in the infant skull and partly because the superior canal lies more nearly in the transverse plane. The lines running forward through the posterior canals of the newborn meet in the region of the

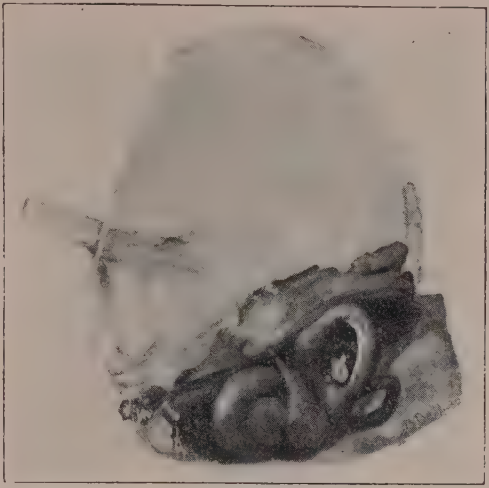


Fig. 194.—Lateral view of temporal bone of newborn child which has been injected with Wood's metal and cleared with Spalteholz's method. (×1½.)

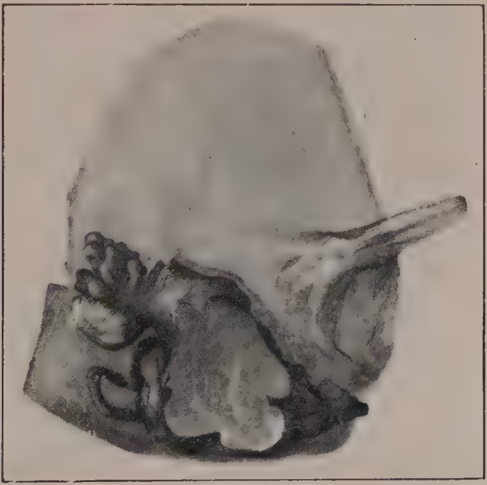


Fig. 195.—Medial view of same specimen as Figure 194. (×1½.)

clivus, while in the adult they meet farther forward in the region of the sella turcica. This is also due to the fact that the posterior canal of

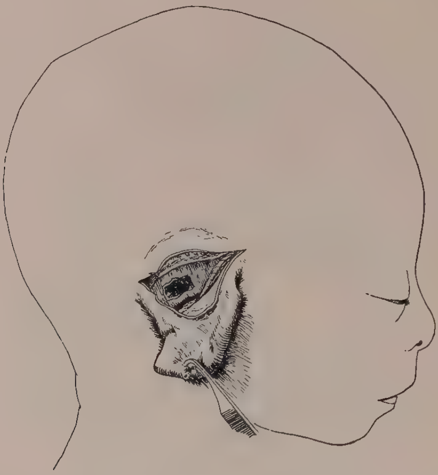


Fig. 196.—Dissection showing position of antrum in relation to external osseous meatus in newborn child.

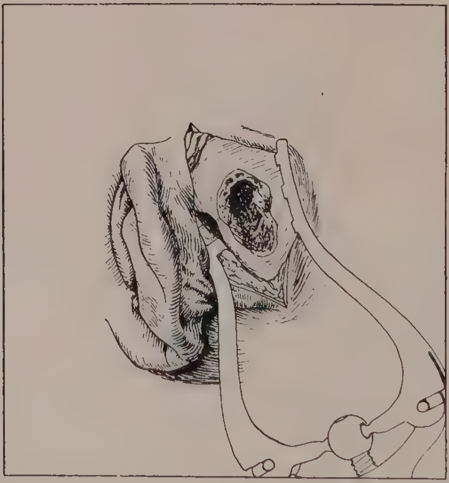


Fig. 197.—Dissection showing position of antrum in relation to the external osseous meatus in the adult.

the newborn lies more nearly in the transverse plane than that of the adult.

Alexander and Shaw found the adult inner ear larger than that of the newborn. Boot found the postembryonic growth to be about 18 per cent. Hyrtl found the inner ear of the adult and child about the

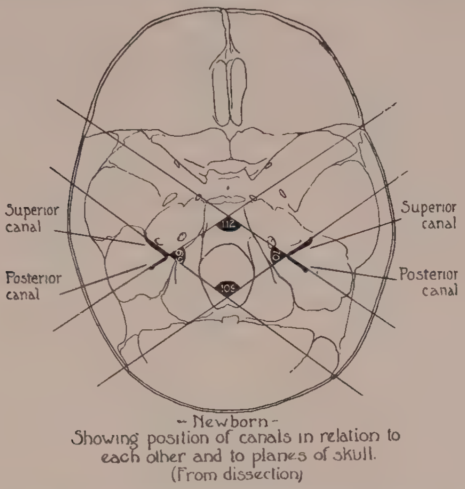


FIG. 198.—Drawing of the base of the skull showing the positions and angles of the superior and posterior semicircular canals in newborn child. (×1½.)

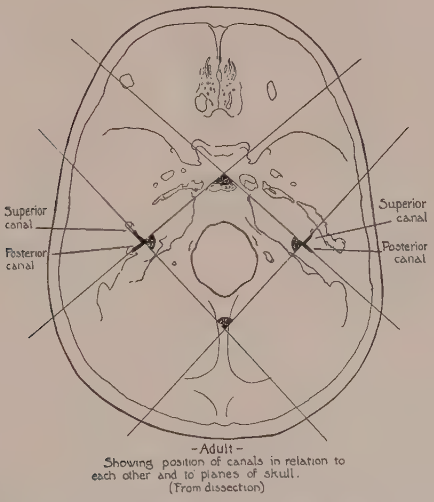


FIG. 199.—Same as Figure 29 of adult skull. (×1½.)

same size, with an increase in size in old age. The diameters at different ages are shown in Tables 3 and 4. The inner ear changes but little in size after the fifth fetal month.

TABLE 3

MAXIMAL LENGTH OF THE INNER EAR, INCLUDING THE COCHLEA, THE VESTIBULE, AND THE POSTERIOR SEMICIRCURAR CANAL

Age.	Author's series, mm.	Length according to:		
		Alexander, mm.	Siebenmann, mm.	Shaw, mm.
Fetal months:				
Five	18			
Seven	18			
Newborn	17	15	19	18
Three years	18			
Five years	16			
Adult	18	18.5	18.5	20

TABLE 4

DIAMETER OF VARIOUS PARTS OF THE INNER EAR AT DIFFERENT TIMES IN PRENATAL AND POSTNATAL LIFE

Age.	Vertical diameter of cochlea, mm.	Horizontal diameter of superior semicircular canal, mm.	Anteroposterior diameter of external canal, mm.	Vertical diameter of posterior canal, mm.
Fetal months:				
Five	7.5	8.0	7.0	8.0
Seven	7.0	7.5	7.0	
Newborn	7.0	8.5	7.0	7.25
Three years	7.5	8.25	7.0	
Five years	7.5	8.5	7.0	8.0
Adult	7.5	8.5	7.0	8.0

The distance of the horizontal canal from the cortex in the infant is from 4 to 6 mm., while in the adult it is from 12 to 20 mm. The horizontal canals and the oval window are the most common points of entrance for infection. The angles of the semicircular canals to each other and their positions in relation to the rest of the skull are shown in Figures 198 and 199.

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MORPHOMETRY OF THE HUMAN FETUS WITH SPECIAL REFERENCE TO THE MEASUREMENTS OF THE HEAD*

LEROY A. CALKINS

A preliminary report of this study was given in Volume one, pages 441–442 of this series. The material there described has been further amplified and strengthened to a total of 369 specimens. The necessary correction for effects of preservation was found by a rather extended series of measurements on fresh specimens, and later on the same specimens during fixation. The effects of birth-moulding were next determined by making a series of measurements on babies born by cesarean section, without the trial of labor, and selected breech extractions. The curves, when finally corrected, resolved themselves into straight lines as previously predicted. The various head measurements, mathematically expressed, are:

Sitting height = 0.66 standing height + 5.0 mm.
Occipitofrontal diameter = 0.235 standing height + 4.0 mm.
Biparietal diameter = 0.19 standing height + 2.0 mm.
Suboccipitobregmatic diameter = 0.2 standing height + 6.0 mm.
Suboccipitofrontal diameter = 0.215 standing height + 7.0 mm.
Occipitomental diameter = 0.235 standing height + 2.0 mm.
Horizontal head circumference = 0.675 standing height + 13.0 mm.
Suboccipitobregmatic circumference = 0.625 standing height + 16.0 mm.
Suboccipitofrontal circumference = 0.65 standing height + 15.0 mm.
Occipitomental circumference = 0.63 standing height + 9.0 mm.
Large circumference = 0.72 standing height + 10.0 mm.

Similar formulæ for other dimensions of the body (as developed simultaneously in this study) enable one to construct an entire fetus at any period of development, if given one of a series of standard dimensions.

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1921. Reprinted from the American Journal Obstetrics and Gynecology, 1922, iv, 109–130. From the Department of Obstetrics and Gynecology and the Department of Anatomy, University of Minnesota, Minneapolis.

Moreover a number of measurements of the body are as valuable in determining age as is the standing or sitting height. A definite roentgenray technic for intrauterine cephalometry is now being developed.

CONCLUSIONS

Measurements of the head, in utero, plotted as ordinates against standing heights as abscissæ for any group of Caucasian fetuses result in straight line curves (this is also true of measurements of other parts of the body).

The relationship between any two dimensions can, then, be expressed by the straight-line, empirical formula: $y = ax \pm b$, (x) and (y) being body dimensions, and (a) and (b) constants.

By study of these formulæ definite mathematical proof is found of the law of cephalo-caudal developmental direction during fetal life.

A definite course of growth, in any dimension, is established by the third month and maintained throughout the remainder of prenatal life.

By the aid of these formulæ, one may accurately construct the external body proportions of a fetus at any period of development, if given any single dimension.

Likewise, one may deduce the size of the head if he can accurately determine any major body measurement in utero. A definite technic for this indirect intrauterine cephalometry is worthy of prolonged intensive study. By such a method one could solve problems of disproportion between passage and passenger, as well as determine viability and maturity with a considerable degree of accuracy.

Birth moulding probably effects greater changes in head dimensions than is ordinarily believed.

Fetuses preserved in formalin, with injection by the method outlined, represent the living fetus in utero better than does fresh or uninjected material.

LIPEMIA RETINALIS. REPORT OF THREE CASES*

HENRY P. WAGENER

Previous to 1922 seventeen cases of lipemia retinalis were reported in the literature. The observations were made without exception in patients with severe diabetes mellitus. In five death occurred within twenty-four hours; in three, within three weeks, and in only two was life prolonged more than three months. One of these patients died in four months. Only two of the patients were females. The ages ranged between fourteen and forty-eight, but only two were more than thirty. The fat in the blood varied from 4 to 26 per cent.

Cases 1 and 3 in the series observed at the Mayo Clinic occurred in young diabetics; Case 2 was a patient with acute lymphatic leukemia. In all there was present the characteristic picture of lipemia retinalis, that is, waxy discs, retinal arteries varying in color from pale salmon-pink to creamy white, veins varying from a light chocolate to creamy white and with difficulty distinguished from the arteries except on and near the disc, smaller vessels practically invisible except as white streaks, and choroid practically undisturbed. In Case 2 there was also marked anemia of the choroid and there were a few small retinal hemorrhages probably due to the anemia.

REPORT OF CASES

Case 1. Mr. C. E. A., aged twenty-six years, was admitted to the Clinic September 9, 1921. The urine contained 3 per cent sugar, and the blood 0.425 per cent sugar an d 8.2 per cent fat; the plasma carbon dioxid was 21.7 volumes per cent. The retinal lipemia had disappeared on the twenty-fourth day after the original observation when the blood contained only 1.9 per cent fat. The patient's present condition is not known.

Case 2. H. C. W., a boy, aged nine years, was brought to the Clinic January 6, 1922. He had acute lymphatic leukemia, with multiple glandular swellings. The hemoglobin was 61 per cent, the erythrocytes numbered 3,160,000, and the leukocytes 51,200 with a marked predominance of lymphocytes. The urine was normal. Following radium applications to the glands, there was diminished leukocytosis but a rapidly progressive anemia. When the erythrocytes had fallen to 1,900,000 and the hemoglobin to 31 per cent, with the leukocytes 24,000 with 87 per cent lymphocytes, lipemia retinalis was discovered, and the blood fat was found to be 5 per cent. Retinal lipemia disappeared on the fifth day after transfusion, but the patient died on the seventh day.

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* Abstract of paper published in full in the American Journal of Ophthalmology, 1922, v, 521–525. From the Section on Ophthalmology, Mayo Clinic.

Case 3. H. S., a girl aged ten years, was brought to the Clinic April 9, 1922. The urine contained 4 per cent sugar and the blood 0.40 per cent sugar and 3.5 per cent fat. The plasma carbon dioxid was 21 volumes per cent. A complete extraction of the fat was impossible in this case because the blood was allowed to clot before the estimation was undertaken. The retinal lipemia disappeared within a week and has not been observed again on repeated examinations. The patient is still in fair health nearly four months later.

CHRONIC SUPPURATIVE OTITIS MEDIA*

HERRMANN E. BOZER

The question of how long conservative treatment should be employed in the management of chronic suppurative otitis media, and when the radical mastoid operation should be performed, has long been debated. In the Mayo Clinic conservative measures of treatment are persisted in as long as there is hope of obtaining a cure. My investigation was undertaken for the purpose of comparing the results of conservative measures of treatment with those of the radical operation, and to ascertain the prognosis when chronic discharging ears were apparently cured by local treatment.

The results of a radical mastoid operation are not uniformly satisfactory. Ruttin, of Vienna, claims only 70 per cent cures of suppuration. Fraser and Garretson obtained 75 per cent cures in 110 cases. They included in this category twenty-four cases in which the mastoid cavities remained moist, but in which there was no actual suppuration. In 22 per cent of their cases hearing was markedly diminished. Stucky reports 89 per cent cures in cases of suppuration. Twenty-one of his 100 patients had diminished hearing after the operation. Undoubtedly the results are not so good in cases in which operation is performed by men of less experience.

The postoperative care of patients with chronic suppurative otitis media is generally long and tedious, as any neglect of the after-care of the ear is very apt to defeat the purpose of the operation. Politzer reports the time of postoperative treatment in his cases to average three to four months. This is about the average time required for a mastoid cavity to become thoroughly healed after a radical operation.

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* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Otolaryngology and Rhinology, 1922. Published in full in Ann. Otol., Rhinol., and Laryngol., 1922. From the Section on Otolaryngology and Rhinology, Mayo Clinic.

The operative mortality in uncomplicated cases is low, about 1 to 2 per cent; permanent paralysis of the seventh nerve occurs in about the same per cent of cases.

Radical operation should be performed only as a last resort, as it results in from 11 to 30 per cent failures to obtain complete cure of suppuration; 20 per cent of patients will have diminished hearing, and the postoperative care will require an average of three months. If more than usual care and persistency will result in the cure of certain cases which, at first, may seem to be refractory, the effort will be well worth while, and the unpleasant features of the radical mastoid operation will be avoided.

A group of 190 selected patients who had received treatment in the Mayo Clinic was studied. All of these patients had been treated within a period of one and one-half years. Treatment was discontinued only when it was believed that no further benefit could be obtained therefrom. In most cases the disease process had apparently been controlled so that the affected ear had remained dry for at least one week before the patient was dismissed from the Clinic. In some cases the ear had refused to become entirely dry. Patients on whom the physician had not been permitted to use every means available, or who had not cooperated to the fullest extent, are not included.

The dry method of treatment was used in all cases. Obstructions to drainage, such as crusted adherent bands and necrosed ossicles were removed as far as possible and daily cleansing of the middle ear and attic regions was instituted after the method of Politzer. No other type of treatment, such as vaccine therapy, ionization methods, roentgen ray, or radium was used. Any disease in the nose and throat was carefully eliminated, and the patient's general condition thoroughly investigated and cared for. The extent of the disease in the affected ears was carefully classified at the time of treatment. The classification is purely empirical and is based on the extent and location of the disease process in the ear. In the main, four types of suppuration were recognized.

Type 1 includes cases in which the discharge was thin, viscid, and mucoid, and arose solely from the eustachian tube. The perforation generally is quite large and is usually situated in the anterior inferior quadrant, although at times the whole of the tympanic membrane may be absent following a former active suppurative process of the middle ear which has since healed.

Type 2 includes cases in which the disease was confined to the hypotympanum and mesotympanum. The perforation of the tympanic membrane may be large or small and situated any place in the pars tensa. The mucous membrane lining the tympanic cavity is often markedly thickened and granular, and secretes thick mucoid fluid containing many leukocytes. Areas of necrosis of the bony walls may be present, and occasionally necrosis of the lower portion of the ossicle may be demonstrated.

Type 3 includes cases in which the suppurative process and necrosis involve the attic and the lower portions of the tympanum. Quite often the perforation of the tympanic membrane is in Shrapnell's membrane and most of the disease is concealed from inspection. Generally, however, the attic seems to be involved secondarily, so that Shrapnell's membrane is intact. A probe introduced from below the level of the anterior and posterior folds will gain free access into the attic and will often dislodge masses of thick discharge, fragments of necrosed ossicles, and portions of cholesteatoma, which have collected in that region.

Type 4 includes cases in which there was definite disease of the antrum and adjacent mastoid cells, besides the Type 3 involvement of the ear. This is sometimes demonstrated by fistulous tracts from the posterior canal wall leading into the mastoid cells, the walls of which are often necrotic or have been eroded by cholesteatoma. Occasionally the aditus ad antrum is so enlarged by cholesteatoma that the anatomic effect of a radical mastoid operation is almost produced. An open tube, contributory to the discharge, may be present in any of the four types.

Ninety-six replies were received from 190 questionnaires. In seventy-eight patients (81 per cent) the discharge had entirely ceased and no apparent suppuration was present when they left the Clinic. In eighteen (19 per cent) the discharge had not entirely disappeared. In forty-two (54 per cent) the ears remained dry, and in thirty-six (46 per cent) they did not. Of the eighteen patients who had left without having the discharge entirely cleared up, the ears of two became dry without further treatment.

Of forty-four patients who attained a satisfactory condition there were twenty-four males and twenty females. The average age was thirty-four years. The average duration of the disease before treatment at the Clinic was about fourteen years, the time varying from two months to fifty years. Of these patients twenty had had constant discharge, while twenty-four had had intermittent discharge, that is, there were intervals during which the ears had apparently been dry. As a rule these periods of quiescence were of short duration, only a few months.

Of patients whose ears did not remain in good condition, there were twenty-eight males and twenty-three females. The average age was twenty-four. The average duration of disease was about twelve years, the shortest being three months and the longest, thirty-six years. Twenty-one patients had had constant discharge and twenty-nine intermittent discharge.

The sex and age do not appear to be factors in the ultimate results. Constancy of discharge does not seem to be an unfavorable factor. It would also seem that a few years additional duration of disease would make but little difference, as the average duration is very long, thirteen years. The average length of treatment of patients who remained in good condition was three and six-tenths weeks. In patients who did not remain in good condition the average duration of treatment was four and seven-tenths weeks. Failure to obtain good results cannot be attributed to less effort spent in treatment.

An attempt was made to determine the effect, if any, that the cause of the suppurative process had on the results of treatment. Many cases were long standing and the patients were unable to recall the exciting cause. The statistics obtained were too meager to justify an attempt to draw any conclusion. It does seem, however, that those cases originating from scarlet fever are very resistant to treatment, and the percentage of failures is as high in this type as in any other type of case.

As I have mentioned, an attempt was made to classify the pathologic condition at the first examination. In order to determine the value of the classification as an aid to prognosis the ultimate results of treatment in each type are tabulated.

The percentage of good results is no higher in Types 1 and 2 than in the more dangerous Types, 3 and 4. The factor tending to cause recurrence of discharge in all types was an open tube. No doubt there are many ears in Types 3 and 4 which, at the time of the patient's report, were discharging only because of an open tube, the attic being in good condition. For these reasons I believe that any classification which fails to consider the patency of the tube offers no aid in the prognosis of the permanency of the cessation of discharge; but I am quite sure that such a classification as I have mentioned does offer a satisfactory method of measuring the danger to life of any particular suppurating ear.

Lillie has recently emphasized that patients who have chronic discharging ears in which a patent tube is a factor should exercise great care in blowing the nose.

In the series of ninety-six patients, eighty-one were careful not to produce undue back pressure in the nasopharynx and eustachian tubes when blowing the nose. Thirty-one per cent reported that such care had a decidedly beneficial effect in preventing their ears from discharging. Twenty-eight per cent were sure it had no effect and 31 per cent were undecided.

Many of the Type 3 ears had open tubes and consequently responded to the precaution in nose-blowing. This is a strong reason for suspecting that many of the Type 3 ears, reported to have begun discharging again after apparent cure, only did so because of open tubes, and not because the old suppuration in the attics had started again. These data also point to the view that the prognosis of cure, that is, permanent cessation of discharge, cannot be based on actual disease in the middle ear and its appendages but, to a large extent, must take into consideration the condition of the tube.

Of the fifty-one patients whose ears were discharging one year after treatment, in twenty-nine the recurrence began with "colds." As the fifty-one cases included fourteen in which cure had not been complete at the time of dismissal, this number must be deducted. Thus, twenty-nine of thirty-seven recurrences (78 per cent) were due to colds and probably the consequent nose-blowing.

CONCLUSIONS

1. About 50 per cent of patients with long standing chronic suppurative otitis media who have responded satisfactorily to treatment, remain in good condition for from one to two and one-half years.
2. Sex, age, and constancy of discharge have no apparent effect on the permanency of the cure.
3. Long duration of discharge is not necessarily an unfavorable factor.
4. The patency of the eustachian tube must be taken into consideration with the type of disease in the ear, if a prognosis of the permanency of apparent cure is given.
5. Local treatment must be well directed and persistent.

6. Care in nose-blowing is an important factor in keeping an ear dry in at least 30 per cent of the cases; this depends on the condition of the tube, and not on the disease in the ear.

7. Many patients who were cured and whose ears remained dry would have had mastoid operations if a conservative view had not been taken and persistent local treatment kept up.

8. It is reasonably safe to assume that the suppurative ear conditions which have responded well to treatment will do so again.

9. Discharge from the tube, after the suppurative process has been controlled, may be considered of minor importance so far as real danger is concerned.

10. Local treatment should be carried out persistently in an effort to obtain satisfactory results, since at least 50 per cent of patients who attain apparent cures by conservative local treatment remain in good condition long enough so that they are unlikely to have serious trouble.

11. The radical mastoid operation, with its accompanying unpleasant features, should be resorted to only in patients in whom there is undoubtedly great danger of intracranial or labyrinthine involvement, and in patients who do not respond satisfactorily to well directed and persistent local treatment.

Results of Treatment

Type.	Good.	Unsatisfactory.
1	6	6
2	24	27
3	13	15
4	2	3

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THE NECESSITY OF ROUTINE FULL MOUTH ROENTGENOGRAMS IN DENTAL DIAGNOSIS*

DONALD C. LYONS

The routine full mouth roentgen-ray examination reveals many dental diseases and anomalies, conditions which for the most part would have escaped notice for many years and continued to act as possible foci of infection, or as accessories in nervous disturbances. Certain of these conditions may be potentially malignant, and if discovered and removed early, will save the patient a great deal of discomfort and perhaps even his life. Five cases illustrative of overlooked dental disease are reported; three of these are reported herewith.

REPORT OF THREE CASES

Case 1 (A383491). Mr. J. A., a man aged forty-two years, came to the Clinic because of poor general health. He was referred to the dental department for examination. Full mouth roentgenograms revealed a large cyst with a calcified center in the region of the lower incisors (Fig. 200). The patient had not noticed pain or any other disturbance in this area. Because of an abscess the right central tooth had been extracted several years before, but evidently all the infection had not been removed. Roentgenograms

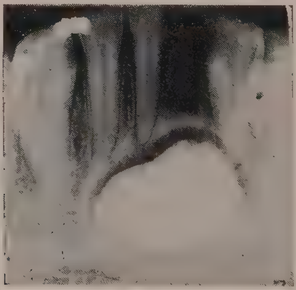

Fig. 200.—Calcified cyst which developed following extraction of tooth with history of abscess.

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* Abridgment of paper published in full in Dental Summary, 1922, xlii, 879–882. From the Section on Dental Surgery, Mayo Clinic.

had not been taken before or after this extraction. It is questionable whether the cyst was present at the time of the extraction, or whether the residual granuloma started it; the latter supposition is the more probable. The cyst had caused the death of the right lateral and the left central teeth and involved the left lateral.

Case 2 (A386093). Mrs. A. T., aged thirty-four years, was examined in the dental department of the Clinic. Roentgenograms showed a well developed area of osteosclerosis between the lower left first and second molars. This condition had been produced partly by malocclusion of the crowns with the opposing teeth and a tight contact (Fig. 201).

Case 3 (A386632). Mrs. H. W., aged twenty-seven years, had fallen down stairs and landed on her face thirteen years before. The lower anterior teeth were loosened by the fall, but soon tightened and appeared to give no further trouble. Full mouth roentgenograms revealed a large area of traumatic necrosis involving the bone around the lower centrals and laterals (Fig. 202). This condition was no doubt the result of the accident and had influenced the patient's general health.

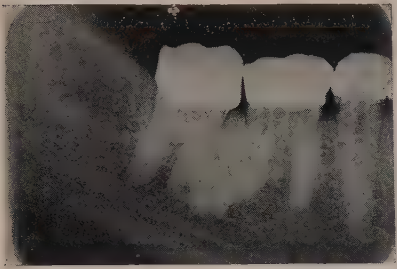

Fig. 201.—Osteosclerosis due to malocclusion.

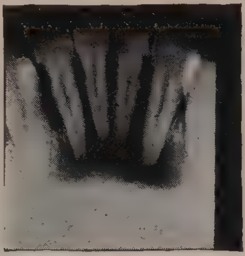

Fig. 202.—Traumatic necrosis of thirteen years' duration.

DISCUSSION

Most chronic abscesses and cysts do not manifest themselves by pain. They progressively destroy the bone a long time before they break into the soft tissue; the patient then notices the swelling caused by the collection of pus or fluid. Without careful full mouth roentgen-ray examinations, checked by second examinations, these and many other dental diseases, as well as anomalies, will escape early attention by the dentist.

The effect of malocclusion and trauma on the peridental membrane and the surrounding process is demonstrated by pain or roentgen-ray examination; only infrequently does pain give warning of the condition that is developing. Pericementitis, hypercementosis, osteosclerosis of the process, pulp stones, and so forth, conditions generally caused by long continued irritation, such as malocclusion, undermine the health of the tooth and may cause the death of the pulp. Occasionally malocclusion or trauma will cause cyst formation or traumatic necrosis; such processes may progress for a long time unnoticed, unless discovered by routine full mouth roentgen-ray examination.

An important factor in the prevention of pyorrhea is the early recognition of predisposing causes. Overhanging fillings, poorly fitted crowns, and inlay attachments of bridge work which do not fit properly, or which stress of mastication has caused to spread, cause irritation of the gums and furnish breeding places for bacteria. Pieces of misplaced and unnoticed filling material are other predisposing factors, as are many other foreign bodies, such as pieces of wooden toothpicks, broken needles used in administration of local anesthetic, and fragments of various substances forced into wounds caused by accidents or explosions (Fig. 203). These conditions break down the resistance of the peridental tissues.

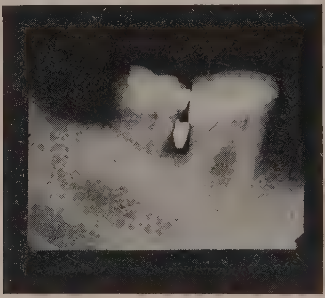

Fig. 203.—Result of misplaced filling material in interproximal space.

A great number of incipient cases of pyorrhea will not be discovered early except by routine full mouth roentgenograms. Figure 203 shows chronic irritation of the gums with subsequent destruction of the alveolar process. It is important in diagnosing pyorrhea pockets by the roentgen ray not to place too much confidence in this proof alone; exploration may be necessary, and it is necessary to distinguish between normal senile atrophy and involvement due to pyorrhea.

In the examination of 400 patients selected at random 1,872 fillings were found. Thirty-one per cent had overhanging cervical margins, and under 63 per cent of these were definite pyorrhea pockets. There were 376 crowns, 52 per cent badly fitted and with rough margins, and under 24 per cent of these were pyorrhea pockets. There were 249 bridges, and 44 per cent were defective; in 57 per cent of these there was pyorrhea around the abutments. In these cases there was no other evidence of pyorrhetic involvement.

Roentgenograms reveal many hidden carious areas. Caries under crowns and fillings, along cervical margins, in proximal surfaces, and in other out of the way places is not noticeable until it causes pain, or enamel caves in. An explorer or floss will generally pass over these areas in their incipiency without obstruction. Only the roentgen ray will reveal them before they can do a great amount of injury to the tooth.

Routine full mouth roentgenograms are a necessity in the diagnosis of oral disease but should not comprise the entire examination. They should be checked and be corroborated by rerays, palpation, exploration, electric sensitivity, and so forth.

ROENTGENOGRAPHIC FINDINGS IN TWO HUNDRED NINETY PARTIALLY EDENTULOUS OR EDENTULOUS MOUTHS*

MATTHEW F. EUSTERMAN

Twenty-eight thousand of the 60,000 patients who registered at the Mayo Clinic in 1920 were sent to the Dental Section for full mouth roentgenograms. The old method for removing teeth did not allow for the elimination of all of the teeth and their associated lesions. Thirty-seven per cent of the areas to which plates were adapted harbored infection in the form of roots, remaining residual areas, and embedded and partially erupted teeth. One hundred twenty-nine roots, evidence of nine residual areas of infection and thirteen embedded and partially erupted teeth are the sum total of roentgenographic findings in 290 edentulous and partially edentulous mouths.

The infrequency with which remaining areas of infection are found will seem negligible to many observers. However, when we take into consideration that these plates have been in place for an average of eight years, thus giving nature sufficient time to throw off any infection that might have been left, due to careless surgical technic, the number of remaining areas in a similar series where extractions were done more recently may approach an appreciable amount. The eighty-nine cases in which 129 roots remained is another factor worthy of consideration. In practically every instance roots that remained following the extraction of teeth gave the same positive results bacteriologically as the pulpless teeth in the same mouth. A typical case follows:

Case 254839. Mr. W. B., aged twenty-three years, registered at the Clinic April 8, 1921, because of marked ocular inflammation. He had taken cold when fishing and the next morning the eye was highly inflamed and painful. Medical examination was negative. Dental examination revealed a lower first molar root.

Diagnosis was made of definite beginning iritis with discoloration of the iris and marked ciliary congestion. The root in question was removed and sent to the laboratory for culture. Iritis was produced within twenty-four hours by intravenous injection into the ear veins of two rabbits.

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* Abstract of paper published in full in Dental Cosmos, 1921, lxiii, 901–903. From the Section on Dental Surgery, Mayo Clinic.

The eye began to clear up immediately following the removal of the root. This is typical of hematogenous infection rather than of a trophic disturbance.

Recently prosthetists have shown that in patients in whom the occlusion deviated from the normal or in patients wearing plates for some time, the backward thrust of the mandible exerting pressure on the auditory canals caused deafness. The onset of the four aural conditions in this series does not allow verification of the fact that tinnitus, and so forth, of which these patients complained, was in any way associated with the extractions.

General examination and final diagnosis in the various gastric conditions do not allow verification of the fact that the digestive apparatus is affected by the removal of teeth.

THE VITAL CAPACITY OF THE LUNGS OF CHILDREN IN HEALTH AND DISEASE*

CHESTER A. STEWART

Observations are reported for 2,509 normal and healthy children, which include 1,289 boys and 1,220 girls from four to nineteen years of age. Observations also are recorded for fourteen boys and twenty-six girls afflicted with mitral insufficiency of varying degrees of severity; for seventeen boys and fourteen girls suffering from acute bronchitis; for four boys and five girls with pneumonia; for thirteen boys and four girls subject to asthma; and for seventy-nine boys and seventy-one girls having tuberculosis. The observations for vital capacity, including both normal children and those with disease, amounts to 1,420 on boys and 1,342 on girls, a total of 2,762 cases.

The vital capacity was measured by means of an accurately calibrated wet spirometer, which offered very little resistance to expiration. The children were carefully instructed to take the deepest possible inspiration, and to empty the lungs completely into the spirometer. As a rule, small groups were taken at a time, so each child understood from observation how to coöperate to the best advantage. Every child was permitted several trials, and the maximum repeatedly expired was recorded as the vital capacity. The children were urged to do their best, and usually the spirit of competition was sufficiently keen to make one reasonably certain that the records obtained represented the best effort they were capable of exerting. In instances in which the coöperation of the child was unsatisfactory the data were discarded. Furthermore, children having an unusually low vital capacity were included in the averages only in case they did not give a history of chronic disease of the heart or lung. So far as possible all children suffering from acute respiratory infections were excluded from the averages. The vital capacities recorded are not corrected for temperature, aqueous vapor tension, or for variations in barometric pressure.

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Pediatrics, 1921. Published in full in the American Journal of Diseases of Children, 1922, xxiv, 451–496. From the Department of Pediatrics, University of Minnesota, Minneapolis.

The children were weighed in their ordinary indoor winter clothing. In order to obtain the net weight, the weight of the clothing (computed as recommended by Bardeen) is deducted from the observed gross weight. The standing height in stocking feet, and also the sitting height, measured with the children seated against a perpendicular scale, were recorded for each in the majority of instances.

In the analysis of the data for the normal children as averaged according to age, standing height, and stem length, in each case statistical methods were employed to calculate the degree each average might be expected to fluctuate if observations were obtainable on an infinitely large number of comparable series of cases, and also to determine the extent of absolute and relative variability of vital capacity, by estimating the probable error and the standard deviation, and by computing the coefficients of variation, respectively.

The possibility of deriving the approximate normal vital capacity for any known age, standing height, sitting height, or weight by means of empirical formula, is discussed.

SUMMARY

At any corresponding age, standing height, sitting height, or body weight the vital capacity of the lungs is constantly greater in boys than in girls, the difference increasing with especial rapidity during the latter half of childhood.

The curves of vital capacity as plotted against age, standing and sitting height, in general, pursue a sinuous course, showing a fairly uniform increase at first, followed later by a period of more rapid growth in lung capacity which later diminishes in rate. The curve plotted against body weight for the boys shows a more uniform course than that for the girls, which has a definitely convex form.

The absolute annual increase in vital capacity in general is fairly uniform during early childhood, increases in rapidity about the time of puberty, and later declines.

The relative increase in vital capacity apparently decreases at first, becomes relatively more rapid about the time of puberty, and then proceeds at a slower rate again. The period of acceleration in the rate of growth in lung capacity begins and terminates at an earlier age in girls than in boys.

Throughout childhood the vital capacity forms a greater proportion of the estimated adult maximum for women (3,200 c.c.) in the girls than in the boys, the adult maximum of the latter being estimated as approximately 4,300 c.c. In general, then, with regard to lung capacity at corresponding ages, the girls may be considered relatively more mature than the boys.

The vital capacity of the lungs apparently reaches a maximum near the twentieth year in boys, and probably slightly before this time in girls.

On using the proper values for the constant, the vital capacity may be computed fairly accurately from the age, the standing height, the sitting height, or the body weight by means of the empirical formula $Y = (AX) \pm b$, Y = vital capacity in centimeters, a = (either age in years, standing height or sitting height in centimeters, or body weight in pounds), X = a constant, and $\pm b$ = a second constant. The proper values for the constants may be determined by referring to the appropriate tables in the complete paper.

The probable error of random sampling increases as the vital capacity increases, but in all instances is relatively small, amounting to less than 25 c.c. as a rule. Therefore, averages obtained from an infinitely large number of comparable series would vary only slightly from those obtained in the present limited series of observations.

The standard deviation (absolute variability), as a rule, increases as the vital capacity increases, and usually is greater in boys than in girls of corresponding age and size.

The coefficient of variation (relative variability) for each sex decreases during early childhood, increases about the period of puberty, and later declines again. The extent of the dispersal of the individual observations from the average, appears to be smaller when averaged in groups differing 5 cm. in standing height or 2 cm. in stem length, than when averaged according to age in years as estimated from the nearest birthday.

The constant relation between the vital capacity and the square of the sitting height, and also between the 0.72 power of the body weight in grams and the vital capacity apparently is not established until the latter part of childhood.

Children may have a normal vital capacity even in the presence of a definite insufficiency of the mitral value, and these children show little abnormal tendency to dyspnea on exertion. In more severe cases the vital capacity is greatly reduced, and the tendency to respiratory embarrassment is proportional to the reduction in lung capacity.

When the condition of the heart improves the vital capacity gradually increases.

Acute bronchitis produces a temporary reduction in vital capacity which, in severe cases, may be very marked.

During the course of lobar pneumonia, even in cases free from pleurisy, the vital capacity rapidly undergoes an enormous reduction. The reduction is altogether out of proportion to the extent of the pneumonic process in the lungs. Following the crisis, the vital capacity gradually returns to normal in a comparatively short time. Physical signs of the disease, however, may disappear before the normal vital capacity is reached. In complicated cases the return of vital capacity to normal may be greatly delayed.

While bronchial asthma may cause an enormous reduction in the vital capacity immediately following an acute attack, nevertheless the reduction promptly disappears as the symptoms subside. Even in children subject to the disease for several years, there is apparently no permanent reduction in the vital capacity of the lungs.

In children with slight evidence of tuberculosis, such as a positive von Pirquet reaction, and a poor health record, and also in children with definite tuberculosis of the bone, the vital capacity is normal as a rule. In a few instances, however, the lung capacity is sufficiently subnormal to lead one to suspect some pulmonary involvement.

In incipient pulmonary tuberculosis the vital capacity may be practically normal, even in the presence of a very active and virulent infection in the lungs. In advanced pulmonary tuberculosis the vital capacity of the lungs is greatly reduced, in proportion to the extent of the disease process.

The abnormal tendency to dyspnea on exertion is much more marked when the reduced vital capacity is caused by disease of the heart, than when caused by disease of the lungs alone, even in instances in which the reductions are similar in extent.

A STUDY OF THE DEVELOPMENTAL TOPOGRAPHY OF THE ORGANS OF THE ABDOMEN WITH PARTICULAR REFERENCE TO THEIR CONGENITAL ABNORMALITIES AND DISPLACEMENTS*

ANGUS L. CAMERON

The topography of fifty selected specimens of the abdominal viscera of human beings in the latter part of the embryonic and fetal period was determined by means of graphic reconstructions with the orthoscopic apparatus and by field graphs of the vertebral levels of the various portions of the abdominal organs.

CONCLUSIONS

1. Taken as a whole the rapid and marked changes in the topography of the abdomen, which are characteristic of early prenatal life, cease with the close of the embryonic period (in the latter part of the third fetal month), and the modifications of the relations and positions of the various abdominal viscera from this time to birth are comparatively small.

2. Most of the abdominal viscera approach the adult position by the beginning of the fetal period. The exceptions to this rule are the organs most affected by the changes of postnatal life, notably the stomach and cecum.

3. The most notable changes in abdominal topography in the fetal period are those produced by the accumulation of material in the cavities of the hollow viscera. In particular, these are the changes in the form of the stomach brought about by the distention of this viscus with mucus or swallowed amniotic fluid, and the changes in the colon and particularly the sigmoid colon through its distention with meconium.

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery, 1921. From the Departments of Surgery and Anatomy, University of Minnesota, Minneapolis.

4. In only one solid viscus, the spleen, was definite evidence noted that the relative increase in the size of the organ distinctly modified its skeletal relations in fetal life. On the other hand, the liver was the only solid organ noted whose relative decrease in size modified its skeletal relation in fetal life, its inferior border moving cranially. The other parenchymatous organs, although growing rapidly, show little modification in their vertebral levels. In other words, the dimensional correlations of the abdominal skeleton and abdominal organs remain fairly constant.

5. The rôle of the liver as a determinant of the abdominal topography in the fetal period seems to have been somewhat overestimated. No evidence was found that the size of the liver had had any effect on the position of the organs which it is presumed to influence, such as the right kidney.

Results of these investigations coincide with the findings of other workers in this anatomical laboratory that the growth of the external proportions of the abdomen follows a constant course in the fetal period. The particular changes enumerated seem to be principally mechanical.

ELEPHANTIASIS: A CLINICAL REVIEW AND AN ATTEMPT AT EXPERIMENTAL REPRODUCTION*

GEORGE D. MAHON

Various definitions of elephantiasis have been given. Practically all refer to the hypertrophy of the skin and subcutaneous connective tissue with vascular disturbances and resulting exudate. The congenital form of elephantiasis usually involves one or more limbs. The pathologic picture differs from the true form in that connective tissue hypertrophy and normal cell infiltration are absent.

No one has been able to obtain cultures of bacteria except during the recurring active cutaneous reactions seen in the majority of cases of elephantiasis. It must be remembered, however, that a few cases of elephantiasis occur without local inflammatory manifestations. Sistrunk had several of this type in his series. Bacteriologic studies were made in most of the cases. In one of these in which there had never been local inflammation, Magath was able to grow, in pure culture, a green-producing streptococcus. In another case, in which there were local manifestations, he was able to isolate practically the same organism from the deep tissues during a period of quiescence.

ETIOLOGIC FACTORS

Manson has traced the life cycle of the filaria which he considered the etiologic factor. Objections have been made because central blockage of the lymphatics cannot produce peripheral edema, and because it has been impossible to find filaria in the blood of patients with well developed elephantiasis, who, at some former time, were known to have been hosts of the filaria. Manson did not attempt to explain the former criticism, but the second issue was well known to him. He believed that the lymph blockage was accomplished by the death of the parent worm, which was caused by the lymphangitis observed in all cases of elephantiasis that he studied. He also believed that trauma to the part harboring the parasite would cause the premature parturition of the ova which, being larger than the embryo filaria and not having power of motion, would cause blockage of the lymphatics.

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota, in partial fulfilment of the requirements for the degree of Master of Science in Surgery, 1921. Reprinted from the American Journal of Medical Sciences, 1922. Copyright by Lea and Febiger, Philadelphia. From the Section on Experimental Surgery, Mayo Clinic.

Blockage of the lymphatics, with subsequent edema, is not sufficient to explain the connective-tissue hypertrophy, which is the most characteristic histopathologic element of the disease. An abundance of experimental proof as well as an enormous amount of clinical material indicate that edema will not excite cell proliferation.

DISTRIBUTION, AGE AND SEX

Elephantiasis has not been recognized as a transmissible disease, although a few reported cases would indicate that it might be. Tuberculosis and syphilis have a questionable relationship to elephantiasis. Operative interference with the inguinal lymphatics has preceded some cases of genital elephantiasis. A preponderance of data favor the idea that the edema and hypertrophy which characterize elephantiasis develop as the result of the action of pathogenic organisms, even though it has not been proved that a specific organism is responsible for the disease. It is the exceptional case that did not begin following lymphangitis, cellulitis, dermatitis, or some manifestation of a local infection. In a few cases onset has been insidious, without symptoms, either local or general, that would lead one to think of an infectious process. This has been observed many times. Webb mentions the same type of case observed by him in India.

Elephantiasis is observed in all parts of the world, but as an epidemic it exists only in certain circumscribed areas in the tropical or subtropical regions. In the United States and Canada it is uncommon and never epidemic.

In the thirty-three cases studied in the Mayo Clinic the youngest patient was twelve, the oldest fifty-five. In tropical countries men are affected more often than women, supposedly on account of injuries and infections to which they are more often subjected. Women and men were affected about equally in the cases reported from the Clinic.

PATHOLOGIC FINDINGS

Most authors have represented the same pathologic findings in elephantiasis. Paget describes elephantiastic tissue as "closely woven and very tough, and on section to exude a whitish fluid." Pusey considers hypertrophy of the subcutaneous tissue the most characteristic feature; he said that the hypertrophy converts the part into a dense fibrous structure in which are usually found dilated lymph spaces. The chorium is greatly thickened, and the matting together of its layers disorganizes its typical arrangement. The epidermis may or may not be thickened. The sebaceous glands, sweat glands, and hair follicles may be unchanged or destroyed. Stelwagon agrees with Pusey that the chief change is hypertrophy of the connective tissue, but he contends that the blood vessels are also changed, and adds that Mosely and Morrison found an increase in the pigment matter. Hartzell draws attention to a plugging of the veins with a thrombus composed of leukocytes. Elliott believes that there are more changes in the arteries than in the veins. Unna believes that the condition begins quite superficially by a blocking of the veins from the inflammatory process excited by the bacteria. There is a subsequent destruction of some of the vessels, with still more edema, and the ever present bacteria, lying latent in the tissue ready to flare up, produce still more hypertrophy of the tissue, thereby interfering more with the circulation. This chain of events continues until finally there is an enormous tissue hypertrophy, with destruction of many superficial blood vessels draining the part, and resulting edema.

In the cases of elephantiasis studied the epidermis was thinned out when the extremity was unusually large. There was always some change in the blood vessels. Occasionally there was a marked thrombosis and lymphocytic infiltration around the vessel, especially in patients who had had violent cutaneous reactions. The lymphocytic infiltration was always mild in the patient who had not suffered from recurring attacks of erythema; but some of the sections representing the most marked hypertrophy were obtained from patients who had never had erysipelas, cellulitis, or any symptom to indicate inflammation in the part. In such cases there was more evidence of lymphocytic infiltration in the deeper layers, and the aponeurosis was often more thickened; also, there were more changes in the blood vessels of the deeper tissues than in the chorium. It may be assumed that in many patients who develop elephantiasis, the inflammatory reaction necessary to produce cell proliferation is caused by low grade organisms confined to the subcutaneous tissue and not of sufficient virulence to produce local or constitutional reactions.

SURGICAL TREATMENT

Mann calls attention to the two principles which, at present, are the basis for the surgical treatment of this condition: (1) establishing new lymph paths, and (2) connecting the edematous elephantiastic tissues with the normal musculature below the aponeurosis.

Sistrunk has performed a modified Kondoleon operation on about forty patients with elephantiasis. He removes, besides the aponeurosis, a wide piece of skin and subcutaneous tissue nearly, though not quite, so wide as the aponeurosis. Recently he has also removed small sections of the aponeurosis in the iliac regions in patients with the disease especially pronounced in the thighs and hips. Sistrunk believes the removal of large pieces of diseased skin and subcutaneous tissue, not capable of functioning because of the destroyed vascular lymph supply, is of great importance.

If these patients are kept in bed for a week or more before operation, the parts will be reduced in size, and operation made easier. Morphin given before operation minimizes the shock. In extreme cases a complete operation cannot be performed at one time, but similar operations on different portions of the extremity may be performed at different times. Operation does not cure elephantiasis, but the condition can be greatly relieved. Better results will be obtained if the patients wear elastic stockings indefinitely, perhaps permanently.

EXPERIMENTS

Since I believed that the hypertrophy and edema which characterize elephantiasis is caused directly by the action of pathogenic bacteria, I attempted to prove it by experiments on dogs. Bockhardt injected a culture of living organisms (the coccus of Fehleisen) into the tissues of a pedunculated malignant tumor, which subsequently took on changes typical of elephantiasis. In a series of experiments on animals an attempt was made to lower the resistance of the part by interfering with the lymphatics draining the region. Later the venous return was also partially ligated further to lower the resistance of the part. The animals were then inoculated with a green-producing streptococcus obtained by Magath from the subcutaneous tissues of two patients in Sistrunk's series. Magath describes the technic used and the type of organism cultured as follows:

"A small piece of tissue taken from the leg (elephantiasis) was introduced directly and immediately into a tube of glucose broth, and incubated for forty-eight hours. At the end of that time a smear made from the broth showed numerous small, short chains of streptococci. Transfers were made by streaking a plate of blood agar; the streptococcus was present in pure culture. The colonies were minute, semi-flattened, and circular, growing slowly with the formation of a slight amount of green pigment, less than *Streptococcus viridans*, but more than typical pneumococcus. The broth culture was used for the first animal injection, and subcultures taken from this in broth were used for subsequent injections. A similar organism was isolated from a piece of tissue taken from the scrotum of another patient with elephantiasis, and this was used for the last series of animal inoculations."

Twenty animals were used. To favor the development of the organism the lymphatics of the groin of the leg were dissected out. In others the femoral vein was also ligated. Controls were used. The injections of the organisms were made intravenously and subcutaneously in different groups of the animals. The intravenous injections were made on the evidence that a blood-borne organism is responsible for the condition. The opposite leg from the one in which the lymphatics or veins, or both, were molested was used for the injection. We undertook this work with the full understanding that the production of a chronic lesion in an animal offered many difficulties. It is well known that animals may not respond to certain organisms as does man. Moreover, the cultures used must be kept under artificial conditions for a long time and would lose some of their activity.

In some of the experiments neither the operative procedure nor the injected bacteria produced any noticeable effect. In many instances the removal of the lymphatics, and particularly the ligation of the venous return, produced edema of the leg for a variable period. The edema did not persist for any great length of time and a condition resembling elephantiasis never occurred. The effect attributable to the bacteria was obtained. The results of the experiments were negative with regard to the production of elephantiasis.

CONCLUSIONS

1. The characteristic feature of elephantiasis is hypertrophy of the collagenous connective tissue with some degree of lymph and venous stasis.

2. The hypertrophy of the connective tissue and the corresponding

stasis are probably the result of repeated insults from pathogenic bacteria.

3. In one group of cases of elephantiasis there is an outward manifestation of infection evidenced by erythema and adenitis. This type is more common. There is a second group in which the disease develops insidiously, and without any local manifestation of infection. From the pathologic study of these cases I am convinced that they too have an infection basis, which is confined to the lower layers of the subcutaneous tissue, and of such low grade as not to excite any local symptom.

4. Anything that causes venous stasis could be considered as predisposing factor in the development of elephantiasis.

5. Central blockage of the lymphatics probably cannot produce permanent peripheral lymph stasis.

6. The parent worm of filaria may excite inflammatory changes, and elephantiasis may be produced in such cases by pathogenic bacteria, the filaria being a predisposing factor.

7. In the Kondoleon operation we have a means of rendering useful service to patients with elephantiasis, although the operation does not positively cure the disease.

8. Elephantiasis can be produced experimentally, although the chief difficulty in producing a chronic lesion is in keeping the organism to be used at a uniform state of virulency.

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GIANT-CELL TUMOR IN THE KNEE JOINT: REPORT OF A CASE*

PIO BLANCO

Xanthic giant-cell tumors are benign. The polynuclear giant cells morphologically resemble the osteoclasts, and their function is probably phagocytic. They may be considered a type of granulation tissue tumor resulting from hemorrhage. The hemorrhage may be caused either by infection or trauma. As a rule, these tumors are located on the extremities and are associated with a tendon or its sheath. Their presence in a joint has not been previously reported.

REPORT OF CASE

Case A339505. Mrs. P. B., aged thirty years, came to the Clinic November, 1920; she had injured both knees by a fall four years previously. There was no immediate disability, but three years later the left knee became painful on use. A smooth, round, firm tumor was felt on the outer side of the ligamentum patellæ. Motions of the knee were normal. Roentgenograms of the knee were negative. On exploration the tumor was found to lie inside the knee joint, and was intimately associated with the infrapatellar fat pad. Microscopically the tissue showed pathologic changes analogous to those found in the xanthic giant-cell tumors described by Broders. The patient's convalescence was uneventful.

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REPORT OF A CASE OF LOOSE OSTEOCARTILAGINOUS BODIES IN THE KNEE JOINT*

PIO BLANCO

The underlying pathologic condition in loose bodies of the joints is far from being recognized. The infectious theory has not been proved. The theory of John Hunter of the transformation of a blood clot in the joint into cartilage is not convincing. The name osteochondromatosis has been suggested by Kopp and Henderson for the type of loose bodies which develop from thickened fringes of the synovial membrane. This has been explained as an inflammatory reaction, but Henderson believes it to be a form of benign new growth of the synovia. Loose bodies may also occur in hypertrophic arthritis, in neuropathic joints, and in the condition described by Koenig, in 1887, as osteochondritis dissecans. He suggested an occlusion of one of the end arteries supplying an area on the mesial surface of the internal condyle of the femur, as the cause. Henderson has observed that most of these changes occur at the insertion of the posterior crucial ligament on the external ridge of the internal condyle, and believes that the constant strain on this ligament by the physiologic action of the knee may be a factor in their production.

The case, as described in detail, illustrates the association of joint changes in a patient with hypothyroidism.

REPORT OF CASE

Case A26042. Miss W. F. C., aged thirty-five years, came to the Clinic July 10, 1909, with symptoms of exophthalmic goiter, for which the superior thyroid vessels were ligated in 1909. Following this operation her general condition improved. In 1920 she returned complaining of limitation of motion and pain in both knees, with attacks of locking and swelling. As a child she had had scarlet fever, complicated by arthritis, involving particularly the knees and feet. She had had acute tonsillitis and influenza on several occasions, and in 1910 the right knee had been injured by a fall.

On examination, there was evidence of hypothyroidism in the slight puffiness of the face, the dry skin, and the dry brittle hair. The pulse, temperature, and blood pressure were normal. The basal metabolic rate was —10 per cent. There was a slight secondary anemia. The leukocyte count was normal and the Wassermann test on the blood was negative. The urinalysis was negative. The tonsils were moderately enlarged and a roentgenogram of the teeth showed one periapical abscess. The knees were normal in appearance, with leathery crepitus on motion, and limited flexion. Roentgenograms of the knees showed marked destructive processes in the condyles of the femurs, and to a lesser extent in the articulating surfaces of the tibias.

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* Abstract of paper published in full in the Journal of Orthopedic Surgery, 1921. From the Section on Orthopedic Surgery, Mayo Clinic.

At operation it was found that the normal convex surfaces of the condyles of the femurs had been changed to concavities, and fringes of synovial membrane hung from both internal condyles. On pressure over these areas loose bodies could be felt. One large loose piece of condyle, 3 cm. in diameter, was removed from the right knee, and two smaller pieces, each 1 cm. in diameter, from the left knee. The condition was thought to be a type of osteochondritis dissecans. Three weeks later tonsillectomy was performed, which was followed by a reaction of fever and joint manifestations. The knees were not involved in this reaction. Convalescence was otherwise uneventful.

CHRONIC ARTHRITIS: A CLINICAL AND BACTERIOLOGIC STUDY OF EIGHTY CASES*

SAM BROCK

This paper is based on a clinical and bacteriologic study of eighty cases of chronic arthritis. The patients were observed clinically in the Orthopedic Section of the Mayo Clinic, and bacteriologically in conjunction with Dr. Meisser in the Division of Bacteriologic Research of the Mayo Foundation. The studies were conducted over a period of eight months, from April to December, 1921. The period of observation was necessarily short in most of the cases. An attempt was made to remove all dental and tonsillar foci of infection and to carry out bacteriologic studies of the foci.

If the changes which take place in the joints in chronic arthritis are regarded as being produced by the same causative agent, and if the clinical variations met with are recognized as merely degrees of the same pathologic process, chronic arthritis will be brought out of its present state of vagueness and hopeless confusion of terminology and classification.

This study does not include cases of acute rheumatic fever or cases of arthritis of acute infectious origin that are sometimes seen during or directly following pneumonia, diphtheria, dysentery, scarlet fever, gonorrhea, syphilis, and so forth, but deals only with cases of chronic arthritis in which a chronic focus or foci of infection have been demonstrated. As a rule, symptoms referable to the joints rapidly subside when an acute infectious process has been overcome, and no apparent damage to the joints can be found. In most cases permanent damage to the joints takes place only after a chronic focus has been established. The acute infections, injury, exposure, chronic constipation, constitutional disturbances, such as take place at the climacterium, and general debility may be prediposing factors in chronic arthritis. A chronic focus, otherwise dormant, may become activated by a sudden lowering of resistance. Any intercurrent infectious disease may aggravate the symptoms in already existing arthritis.

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Billings, in 1912, enumerated most of the possible sites of focal infection. Chronic foci may exist in several places in the body at the same time, and not be revealed by a most careful search. Ely, in 1917, emphasized the importance of teamwork in the search for possible foci of infection. A careful history and a routine, systematic examination are essential in every case of chronic arthritis, whether or not there are symptoms pointing to a possible focus. A Wassermann test and roentgenograms of the sinuses should be a part of every examination.

Gouty and hemophilic diatheses have been recognized for a long time. A diathesis in chronic arthritis, however, has not been generally accepted, although some investigators claim that the familial disposition is of more importance than the specificity of the infecting bacteria. Our studies have led us to believe that heredity plays an important part in chronic arthritis and that some persons have a lower joint resistance than others. Fifty per cent of our patients gave a family history of arthritis. Billings has suggested that some protective agent might be present in certain persons.

There were fifty-five females and twenty-five males in the series of eighty cases. Garrod reported a proportion of five females to one male. Boorstein reported sixty-five females to forty males.

Bacteriology.—The technic employed in bacteriologic studies was the same as that carried out by Rosenow in his studies on elective localization of streptococci. Every devitalized tooth was removed, whether evidence of infection in the roentgenogram could or could not be demonstrated. Cultures made from the roentgenologically positive and negative devitalized teeth yielded the same type of microörganisms, which on animal inoculation had the same selective action for joints.

The low percentage of positive results in the studies on the tonsil may be explained in part by the practice in the Clinic of performing tonsillectomy in every case of arthritis, if the general condition of the patient does not contraindicate the operation. It is a well known fact that the small, flat, fibrous, buried type of tonsil, which may appear quite harmless, has often been demonstrated to be the chronic focus of infection. The importance of a clean tonsillectomy cannot be over-

TABLE 1

Eighty Cases of Chronic Arthritis

	Cases.	Per cent.
Proliferative	50	62.5
Degenerative	24	30.0
Spondylitic	6	7.5

TABLE 2

Ages by Decades

	Proliferative arthritis.		Degenerative arthritis.		Spondylitic arthritis.		Total.	
	Pa-tients.	Per cent.	Pa-tients.	Per cent.	Pa-tients.	Per cent.	Pa-tients.	Per cent.
1 to 10 years	.....	.....	1	4.16	..	.....	1	1.25
11 to 20 years	5	10.00	..	.....	..	.....	5	6.25
21 to 30 years	10	20.00	6	25.00	3	50.00	19	23.75
31 to 40 years	19	38.00	4	16.66	2	33.33	25	31.25
41 to 50 years	9	18.00	4	16.66	1	16.66	14	17.50
51 to 60 years	6	12.00	8	33.33	..	.....	14	17.50
61 to 70 years	1	0.196	1	4.16	..	.....	2	2.50

TABLE 3

Average Duration of Chronic Arthritis

	Months.
Proliferative	54.46
Degenerative	96.75
Spondylitic	58.16
Total average	67.42

estimated, as even the smallest tag may continue to act as a chronic focus of infection. It is impossible to obtain pure cultures from extirpated tonsils. The contaminating bacteria may completely overgrow the infecting microörganisms. A negative result, therefore, would not detract from the possibility of the tonsils acting as a chronic focus. A third factor might be ascribed to the interval which elapsed following the extractions of teeth before tonsillectomy was performed. It is possible that sufficient antibodies are produced during this interval to attenuate the virulency of the invading bacteria and thus prevent a positive result in cultures from the tonsils which were acting as a chronic

TABLE 4

PREDISPOSING FACTORS IN CHRONIC ARTHRITIS

	Proliferative.		Degenerative.		Spondylitic.		Total.	
	Patients.	Per cent.	Patients.	Per cent.	Patients.	Per cent.	Patients.	Per cent.
Infected teeth......	40	80.00	20	83.33	5	83.33	65	81.25
Infected tonsils.....	31	62.00	14	58.33	3	50.00	48	60.00
Constipation.......	16	32.00	11	45.83	1	16.66	28	35.00
Endometritis and endocervicitis....	16	32.00	6	25.00	..	.....	22	27.50
Exposure..........	11	22.00	5	20.83	..	.....	16	20.00
Influenza..........	5	10.00	..	.....	..	.....	5	6.25
Cholecystitis.......	2	4.00	2	8.33	..	.....	4	5.00
Injury............	1	2.00	2	8.33	1	16.66	4	5.00
Infection of an antrum............	2	4.00	..	.....	..	.....	2	2.50
Exophthalmic goiter	2	4.00	..	.....	..	.....	2	2.50
Menopause........	1	2.00	1	4.16	..	.....	2	2.50
Not stated.........	3	6.00	1	4.16	..	.....	4	5.00

Eight patients with proliferative arthritis gave pneumonia, low resistance, "cold," hard work, infections of the sinus and of the ear, fissure, and hemorrhoids, respectively, as predisposing factors.

TABLE 5

CONDITION OF PATIENTS ON ARRIVAL AT THE MAYO CLINIC

	Proliferative arthritis.		Degenerative arthritis.		Spondylitic arthritis.		Total.	
	Patients.	Per cent.	Patients.	Per cent.	Patients.	Per cent.	Patients.	Per cent.
Worse............	42	84.00	17	70.80	4	66.66	63	78.75
Standstill..........	3	6.00	6	25.00	2	33.33	11	13.75
Better............	5	10.00	1	4.16	..	.....	6	7.50

focus. It has often been observed that, with the extraction of teeth, the animals subsequently inoculated showed less joint involvement than those inoculated with cultures from the teeth first extracted.

TABLE 6

RESULTS OF PREVIOUS TREATMENT

	Proliferative arthritis.		Degenerative arthritis.		Spondylitic arthritis.		Total.	
	Patients.	Per cent.	Patients.	Per cent.	Patients.	Per cent.	Patients.	Per cent.
With previous treatment	35	70.00	14	58.33	3	50.00	52	65.00
With improvement.....	11	31.42	4	28.57	1	33.33	16	30.77
Improvement by tonsillectomy.........	7	63.63	..	.....	1	.....	8	50.00
Dentistry...........	3	27.27	4	.....	..	.....	7	43.75
Tonsillectomy and dentistry..........	1	9.09	..	.....	..	.....	1	6.25
With no improvement...	24	68.57	10	71.42	2	66.66	36	69.22
Improvement by tonsillectomy.........	13	54.16	7	70.00	..	.....	20	55.55
Dentistry...........	5	20.83	3	30.00	2	.....	10	27.77
Tonsillectomy and dentistry..........	5	20.83	..	.....	..	.....	5	13.88
Mastoidectomy and operation on the gallbladder........	1	4.16	..	.....	..	.....	1	2.77

It would seem from a clinical study that a chronic focus or foci anywhere in the body might be the cause of chronic arthritis. Further study along bacteriologic lines will be necessary to emphasize the importance of foci other than the teeth and the tonsils in chronic arthritis.

The pathology of chronic arthritis has been accurately and comprehensively described by Nichols and Richardson in 1909, by Pommer in 1912, and by Nathan in 1917. The pathologic classification of Nichols and Richardson has been taken as a basis for our clinical and bacteriologic studies. The cases are divided, therefore, into fifty of the proliferative type of arthritis and twenty-four of the degenerative type. Six cases of spondylitis are discussed separately.

CHRONIC DEGENERATIVE AND PROLIFERATIVE ARTHRITIS

Differentiation.—The Roentgenologic Section at the Mayo Clinic reports the articular changes seen in chronic arthritis as slight, hyper-

TABLE 7

TREATMENT AT THE MAYO CLINIC

	Proliferative arthritis.		Degenerative arthritis.		Spondylitic arthritis.		Total.	
	Patients.	Per cent.	Patients.	Per cent.	Patients.	Per cent.	Patients.	Per cent.
Dentistry	24	48.00	7	29.16	2	33.33	33	41.25
Tonsillectomy and dentistry	12	24.00	8	33.33	3	50.00	23	28.75
Tonsillectomy	10	20.00	7	29.16	1	16.66	18	22.50
Tonsillectomy, dentistry, and drainage of antrum	0	.....	2	8.32	..	.....	2	2.50
Dentistry and radical operation on the antrum	1	1.96	..	.....	..	.....	1	1.25
Drainage of antrum	1	1.96	..	.....	..	.....	1	1.25
Dentistry and hemorrhoidectomy	1	1.96	..	.....	..	.....	1	1.25
No treatment	1	1.96	..	.....	..	.....	1	1.25

trophic, and destructive. These are objective, morphologic findings and are of value only after definite changes in the joints have taken place. A roentgenographic report of slight arthritis is not sufficient to distinguish between the two types of chronic arthritis. The term "hypertrophic" is in itself misleading, as it is employed to describe bony proliferations which are met with in variable degrees in both processes. Therefore, the clinical history and the physical findings must be depended on in making a differential diagnosis in the very early cases. Fifty-three positive and twenty-one negative roentgenologic interpretations were made in the series of seventy-four cases. In twelve of the fifty-three in which the roentgenograms were positive, there were slight cartilaginous or bony changes; fibrous ankylosis was present in six cases of these twelve. Of the twenty-one cases in which the roentgenograms were negative, fibrous ankylosis was present in six. There remain, therefore, twenty-one cases in which the arthritic process had not yet produced sufficient osseous change that the character of the lesion could be determined. Twenty of these have been classified as proliferative arthritis, and one as degenerative, on the clinical history and physical findings alone.

TABLE 8

A Bacteriologic Study of Infected Teeth

	Teeth.		Cultural results.		
	Condemned.	Cultured.	Pure streptococcus.	Streptococcus and staphylococcus.	Streptococcus, staphylococcus, gram-negative, gram-positive, and gas-producing bacilli.
Thirty-five cases of proliferative arthritis					
Pulpless, roentgenograms positive....	64	26	16	9	1
Pulpless, roentgenograms negative....	42	32	24	7	1
Putrescent pulps..................	15	11	10	..	1
Extensive pyorrhea................	3	2	2		
Roots..........................	3	1	..	1	
Impacted.........................	2	1	1		
Residual granuloma...............	1	1	1		
Extensive caries..................	1	1	1		
Total..........................	131	75	55	17	3
Seventeen cases of degenerative arthritis					
Pulpless, roentgenograms positive....	40	31	22	7	2
Pulpless, roentgenograms negative....	17	10	6	4	
Putrescent pulps..................	5	3	2	1	
Extensive pyorrhea................	6				
Roots..........................	3	1	1		
Residual granuloma...............	1	1	1		
Extensive caries..................	1	1	1		
Total..........................	73	47	33	12	2
Five cases of spondylitic arthritis					
Pulpless, roentgenograms positive....	7	5	4	1	
Pulpless, roentgenograms negative....	3	3	2	1	
Putrescent pulps..................	3	2	..	2	
Total..........................	13	10	6	4	

TABLE 9

Results in Animals Following Injection

Cultures obtained from infected teeth in cases of chronic arthritis.

	Cases.	Animals injected.	Percentage incidence of lesion.						
			Joints.	Muscles.	Kidneys.	Stomach.	Endocardium.	Myocardium.	Bladder.
Proliferative........	35	102	57	30	4	4			
Degenerative........	17	58	57	29	16	7	2	4	
Spondylitic.........	5	13	69	6	..	2			
Cultures obtained from tonsils in cases of chronic arthritis.									
Proliferative........	18	45	22	11	13	6	..	..	4
Degenerative........	12	28	18	7	..	7	7		
Spondylitic.........	3	7	60	14	14	14			

There are no hard and fast rules of differentiation in the clinical course of proliferative and degenerative arthritis. In the very early stages of the disease it is almost impossible to distinguish between the two types. In each the onset may be stormy or insidious and the progress may be with or without exacerbations. Ninety per cent of the eighty patients in the series gave histories of gradual onset of symptoms. As a rule the onset in proliferative arthritis is more acute, and the progress of the disease is accompanied by exacerbations more or less severe.

As a rule, degenerative arthritis has an insidious onset and pursues a slow, progressive course without definite exacerbations and without marked constitutional symptoms. In the proliferative type there may be slight elevation of temperature during the attack and the affected joints may present all the signs of acute or subacute inflammatory reaction. In this series the temperature was recorded while the patients remained under observation from one to six weeks, and it was found to be normal in all but a few; none had a temperature above 100 except the few who experienced reactions following the removal of foci of infection. The pain may be so severe that the patient is completely incapacitated for several days. The process may be confined to one or more joints for a variable length of time, but it tends toward polyarticular bilateral involvement and true fibrous and bony ankylosis. The joints may be spindle shaped, especially in the proximal interphalangeal articulations of the fingers. The enlargement is due to the swelling of periarticular tissues. Myositis and neuritis were present in 16.32 per cent of the cases of proliferative arthritis, and myositis alone in 40.8 per cent. In only one case of degenerative arthritis was a history obtained of myositis and neuritis associated with arthritic symptoms.

In degenerative arthritis one or more joints may be affected, but there is a little tendency to rapid joint involvement. The arthritic process may, in fact, remain confined to one or more joints, particularly the hip or knee. Petrin and Johansson, in 1921, found that in cases of chronic arthritis of the hip joint both joints were affected in ninety of the 103 cases. Ely regards monarticular involvement as probably only apparent. Monarticular or oligo-articular degenerative arthritis does not lead to fibrous or true bony ankylosis. If ankylosis should occur, it is through interlocking of the ends of the joint, causing ankylosis by deformity. The joints are nodular and not fusiform, as in the proliferative type. The appearance of any arthritic joint depends on the predominance of the proliferative or degenerative process in the joint, the duration of the disease, and the injury to the joint.

Whether a proliferative or a degenerative process in the joint is in the ascendency would depend on the degree of virulency of the invading bacteria and the susceptibility of the joint tissues to the microörganisms. If the bacteria is highly virulent and the joints affected respond actively to the stimulus, a proliferative process is most likely to ensue. In the degenerative type of arthritis the virulency of the bacteria is low and consequently response of the joint structures is relatively inactive.

In the proliferative arthritis of this series the sequence of joint involvement was knees, fingers, ankles, wrists, elbows, spine, hips, and temporomaxillary joints. In the degenerative type the sequence was fingers, knees, wrists, hips, elbows, spine, temporomaxillary, and sternoclavicular joints. There was a tendency toward symmetrical involvement in all cases.

Pain a symptom.—Pain in the joints was a variable symptom, present to some extent in 62 per cent of the patients with the proliferative type and in 33 per cent with the degenerative. The pain was constant in 18 per cent with the proliferative type and in 16.6 per cent with the degenerative; it was present only with exacerbations of joint symptoms and on motion in 44 per cent with the proliferative and in 16.6 per cent with the degenerative. The pain naturally depended on the activity of the arthritic process, and varied from merely stiff aching to acute pain. In many cases the pain shifted from joint to joint.

Effect of the weather.—Fifty per cent of the patients with the proliferative type of the disease and 25 per cent with the degenerative were affected by changes in the weather. Forty per cent of all patients had been affected by some change in the weather, 31.25 per cent had not noticed differences in joint symptoms, 11.25 per cent had been worse in cold weather, 13.75 per cent had been worse in cold, damp weather, and 3.75 per cent had been worse in the spring and summer months.

The research of Nichols and Richardson has shown that the blood supply of the joints is relatively poor, the synovial membranes receiving their nutrition indirectly from the synovial fluid. Barcroft has shown that the blood carries about forty times as much oxygen as the same volume of plasma, and that reduction of temperature lowers the dissociation curve of hemoglobin and oxygen. The decreased oxygen tension would produce ideal conditions for the growth of selectively aërobic bacteria in and around the joint structures, as has been shown by Rosenow. Cole and Blake have shown that the pneumococcus and *Streptococcus viridans* convert hemoglobin into methemoglobin, thus inducing suboxidation. Forty per cent of the patients had been able to foretell a change in temperature by a sudden activation of joint symptoms.

Effect of removal of foci of infection.—The reaction experienced by a patient with arthritis following the removal of a chronic focus may be regarded as an indication of the degree of virulency of the invading bacteria. The reaction is described by the patient as simulating an exacerbation of the joint pain. It is usually transitory, disappearing, as does the exacerbation, within two or three days. The reactions vary from a slight stiffness in one or more joints to more severe joint pain and systemic disturbances with elevation of temperature.

Following the removal of a chronic focus, 25 per cent of our patients experienced a negative phase, having had almost complete relief of all joint symptoms, symptoms more or less severe in 15 per cent. Lillie and Lyons reported that 55.3 per cent of their patients improved immediately after tonsillectomy; 12 per cent had acute exacerbations of joint symptoms. Fatalities have been known to occur following the removal of chronic foci during a period of activity of the arthritic process. This exacerbation might be attributed to the sudden shower of bacteria thrown into the circulation. The reaction has been observed particularly when sockets of teeth containing large granulomas have been thoroughly curetted. Pemberton has attributed the negative phase, or amelioration of symptoms, following the removal of a chronic focus of infection to postoperative starvation. This does not, however, seem to account for the transitory lapse of symptoms in many cases, as the period of starvation is entirely too short.

Cardiac disorders.—Many investigators have called attention to the absence of cardiac disease in chronic arthritis. There was no evidence of the disease in the series of eighty cases.

SPONDYLITIC ARTHRITIS

The joints of the spine are subject to the same proliferative and degenerative changes in chronic arthritis as those which take place in the other joints of the body. The disease may begin in the small joints of the articular processes and the costovertebral articulations, or it may be confined largely to the intervertebral discs. The spine is usually involved throughout its length when the small articulations are affected, but it is rarely thus involved when the arthritic process is limited to the intervertebral discs. The erosion which takes place in the discs leads eventually to approximation of the bony segments. The round, lateral borders of the bodies of the vertebræ are sometimes replaced by irregular exostoses and the spiky prolongations thus formed sometimes fuse and produce the complete rigidity of the so-called poker spine.

Arthritis may be confined entirely to the spine or the large joints; the shoulder, hip, or knee joints may be simultaneously affected. The involvement of large joints often precedes the spondylitis. McCrae reports that in thirty-nine of eighty-one cases of spondylitis the spine alone was involved, and in forty-two arthritis in other joints was associated.

Beer was the first to call attention to involvement of the muscles and tendons near the affected vertebræ. These structures may be affected quite early and may well explain why roentgenograms in the early stages of the disease show little or no bony changes, even though complete ankylosis is present. The anterior common ligament has been shown by Ruffer and others to be the first affected. Ossification of the supraspinous ligament alone is sufficient to prevent all movements of extension and flexion.

Bechterew, Strümple, and Marie were the first to describe in detail the neurologic phenomena in spondylitis. Occasional motor disturbances with cramp-like twitchings of the hands and feet and contractures of the extremities were present in some cases; in others marked muscular atrophy and paretic weakness of the extremities were noted, while in still others few or no atrophic changes were observed.

Sensory disturbances: pain, hyperesthesias, analgesias, atrophic changes in the skin, edema, increase of tendon reflexes, and so forth, have also been observed.

Six patients (7.5 per cent) of the eighty of the series had spondylitis; all were males.

There was a family history of arthritis in 50 per cent of the cases. Both Bechterew and Marie have called attention to the hereditary tendency in spondylitis. The onset of symptoms had been gradual in each case.

Arthritis of the large joints had preceded that of the spine in five cases. The small joints were not involved in any case. In only one case was there joint involvement other than of the spine. There was bilateral involvement of the shoulder joints in three cases, and bilateral involvement of the hip and knee in two.

The onset of symptoms began in the third decade in three cases, in the fourth decade in two, and in the fifth decade in one. The duration of the disease averaged fifty-eight and one-tenth months.

In four of the cases there were variable degrees of muscular atrophy, pain of more or less severity, areas of hyperesthesia, increase in tendon reflexes, and general weakness. In two cases there were no symptoms other than increasing stiffness of the spine. The pain was localized chiefly in the muscles of the back, shoulder, and lumbar regions; it had been constant and severe enough to require opiates at times in two cases. In one case there had been pain only with motion, and in one only with exacerbations, while in two cases there had been no pain. The symptoms had been aggravated by changes of the weather in three cases.

Four patients had become very nervous; they had lost much strength and weight and their symptoms were becoming progressively worse. The greatest loss of weight had been 46 pounds, the least 10 pounds, an average of 27.5 pounds. Five patients gave histories of dental infection, one of chronic constipation, and one of injury. Three patients had received previous treatment elsewhere by the removal of foci of infection; one had improved for a short time following tonsillectomy.

In only two instances were osseous changes shown in the roentgenograms, although the spine was affected throughout its length in five.

PROGNOSIS

Hammond, in 1918, sent out questionnaires to 177 orthopedic surgeons, asking for information regarding end-results following the removal of chronic foci of infection in chronic arthritis. The consensus of opinion was that improvement and cure have been obtained in many cases, but that the beneficial results were more in evidence in the acute cases than in the chronic. Patients with acute onset came earlier for treatment than those with insidious onset and without constitutional symptoms. The former, therefore, have the best prospects for early eradication of the focus or foci of infection. Nevertheless, many cases of chronic arthritis must be regarded as incurable. In spite of the removal of every demonstrable focus of infection and the general measures resorted to, the disease progresses with relapses until the patient becomes helpless. The duration of the disease cannot be established. In some cases, especially those of the oligo-articular degenerative type, the disease may come to a standstill or improvement take place, even though nothing is done to stop its progress.

Jones, Bassler, Hartzell and Henrici, and others have called attention to the fact that patients with chronic arthritis often suffer relapses over a period of years. The relapse may be associated with colds, coryza, pharyngitis, and so forth. During the longer intervals of quiescence of joint symptoms it may be thought that the arthritis has entirely subsided. Once the joint has become sensitized to the infection, however, even though the chronic focus has been removed, the exacerbations of symptoms may continue. The joint may in itself act as a secondary focus for subsequent joint involvement. Other secondary foci in the gallbladder, in the appendix, or elsewhere in the intestinal tract may suffice to keep the arthritic process activated.

Cases in which bony changes are shown in roentgenograms are least favorable from a prognostic standpoint. Nichols and Richardson have shown that restoration of the articular cartilage is rare, as cartilage has relatively little power of repair. The mechanical interference with joint function, therefore, will persist in spite of the fact that every focus of infection has been removed.

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VII

BRAIN, SPINAL CORD, AND NERVES

THE DEVELOPMENT OF THE EYEBALL AND OPTIC NERVE IN THE FETUS WITH PARTICULAR REFERENCE TO CHANGES IN SIZE, FORM, AND POSITION*

ELLERY LESLIE ARMSTRONG

The growth of the eyeball and optic nerve in prenatal life was determined by the quantitative study of these structures in a series of seventy-one human fetuses ranging in total body length from 7.5 to 52.5 cm., and in age from about ten weeks to birth. Measurements were made of the volume and various axes of the eyeball, the height and breadth of the cornea, the length, diameter, and angle of the optic nerve, the size of the various segments of the eyeball in relation to the entrance of the optic nerve, and the distances separating various segments of the two eyeballs. In all, about 1,400 quantitative determinations were made from this material. The data thus secured were analyzed by the use of graphic methods and by the development of empirical formulæ. The chief findings were as follows:

The growth in volume of the eyeball in the fetal period agrees very closely with that of the brain-stem and spinal cord. The growth of the diameters of the eyeball is also very like the lineal growth of the brain-stem and spinal cord and may be expressed by the same general empirical formula: $Y = a\,[(bX)^c \pm d]$, in which Y is the dimension in question, X the body length and a, b, c, and d are constants. The postnatal growth of the eyeball follows more closely that of the cerebrum than that of the brain-stem or spinal cord. The postnatal growth in volume of the eyeball seems to have been distinctly overestimated; the data indicate that the postnatal gain is not more than 120 per cent. The eyeball diameters increase 35 to 40 per cent in postnatal life. In the latter part of fetal life the temporal segment of the eyeball grows more rapidly

* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science, 1921. From the Department of Ophthalmology and Otolaryngology and the Department of Anatomy, University of Minnesota, Minneapolis.

than the nasal segment. The fetal growth of the diameters of the cornea is not like that of the eyeball as a whole, but resembles the growth of the external dimensions of the body. It may be expressed by the general empirical formula for external dimensions: $Y = aX \pm b$ (symbols in formula above). The fetal growth in length and diameter of the optic nerve bears a simple relation to the increase in body length and may be expressed by the formula quoted.

During fetal, and probably early postnatal life, the eyeballs undergo great changes in position. Three epochs can be recognized in these changes. In the first period, from the end of the first to the end of the third fetal month, the eyeballs converge toward one another through an angle of 80 degrees. In the middle period, from the end of the third to the end of the eighth fetal month, the convergence is continued at a slower rate and the angle of the optic nerves is reduced by 25 degrees. In the third period, extending from the eighth fetal month to an unknown time in childhood, the angle is very slowly reduced, the entire reduction in this epoch being not over 10 degrees.

The data indicate that the changes in the axes of the eyeballs and optic nerve are not dependent primarily on the changes in the bony orbit. Most of the convergence of these structures takes place before the ossification of the orbit is well under way and even before this cavity is completely outlined in bone or cartilage.

The process of the convergence of the eyeballs seems to be quite variable in individual cases and it is possible that certain cases of strabismus may be explained on the basis of this variation. Thus an arrested convergence might account for a divergent strabismus and an excessive convergence might account for a convergent strabismus.

A STUDY OF FOUR CASES OF GLOSSOPHARYNGEAL NEURALGIA*

JOHN B. DOYLE

Sicard and Robineau have described three cases of what they termed "algie vélopharyngée essentielle." All of the patients had paroxysmal pain of excruciating severity in the throat. These authors reported cures of three and four years' duration, following section of the ninth and the pharyngeal branches of the tenth nerves, and ablation of the superior cervical sympathetic ganglion. Under the title "Glossopharyngeal neuralgia," Harris has recently described two cases of paroxysmal pain in the throat which radiated to the ear.

Doyle reports four cases of similar nature observed at the Mayo Clinic between March 14 and June 1, 1922. The first patient was a man, aged sixty-three years, who had attacks of paroxysmal pain of great severity for periods of months in the past five years. The pain was paroxysmal, sharp, and agonizing; it arose in the right faucial region and radiated laterally to the area anterior and posterior to the right ear. Resection of the posterior root of the gasserian ganglion gave but temporary relief. Evulsion of the ninth and section of the pharyngeal branch of the tenth nerves have been followed by relief to date.

The second patient was a man, aged fifty-two years, who complained for two weeks of a dull throbbing pain in the region anterior to the right external auditory meatus, associated with paroxysms of sharp, stinging pain in the right side of the throat and right ear. Injection of the mandibular division of the fifth, and the auriculotemporal nerve did not influence the pain.

The third patient was a woman who had been well until the summer of 1921 when she developed occasional, mild, paroxysmal pains lasting a second or two, originating in the right side of the throat and radiating to the angle of the right mandible. After six weeks the pains disappeared only to return April 10, 1922, following a drink of cold water. The paroxysms are of moderate severity and occasionally occur in series.

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* Abstract of paper published in full in the Archives of Neurology and Psychiatry, 1923, ix, 34–46. From the Section on Neurology, Mayo Clinic.

The fourth patient was a man aged sixty-one, who had attacks of paroxysmal, sharp, stabbing, stinging pain lasting a few seconds in five periods of about ten days, during the past nine years. The pain was in the region inferior and posterior to the left external auditory meatus, and was associated with a sense of irritation in the left lateral pharyngeal region.

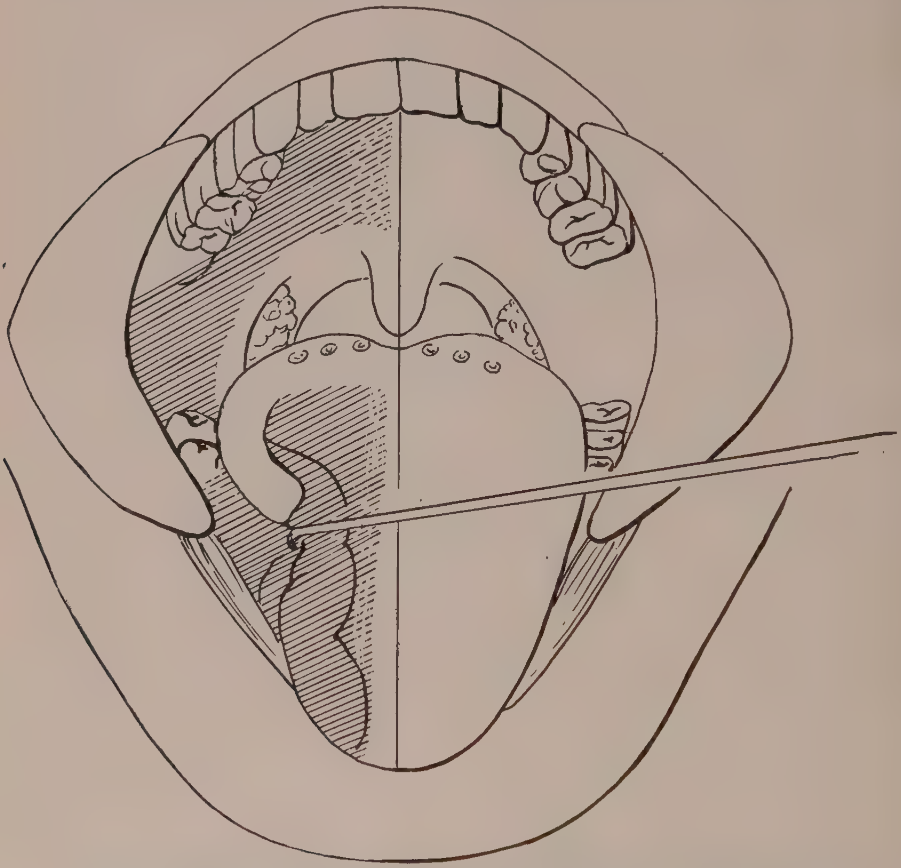

Fig. 204.—Shaded area shows distribution of postoperative anesthesia to touch, pain, and temperature over tongue, hard palate, and anterior part of soft palate in the right, in a case of trifacial neuralgia.

Following section of the posterior root of the gasserian ganglion, and evulsion of the ninth and section of the pharyngeal branch of the tenth nerves on the right side in the first patient, there was complete anesthesia to tactile, pain, and temperature sensation over the cutaneous distribution of the right fifth nerve, as well as over the mucous membrane of the right half of the buccal cavity, the right half of the alveolar processes, the tongue and hard palate, the anterior half of the right nasal cavity, and all of that portion of the pharynx lying between

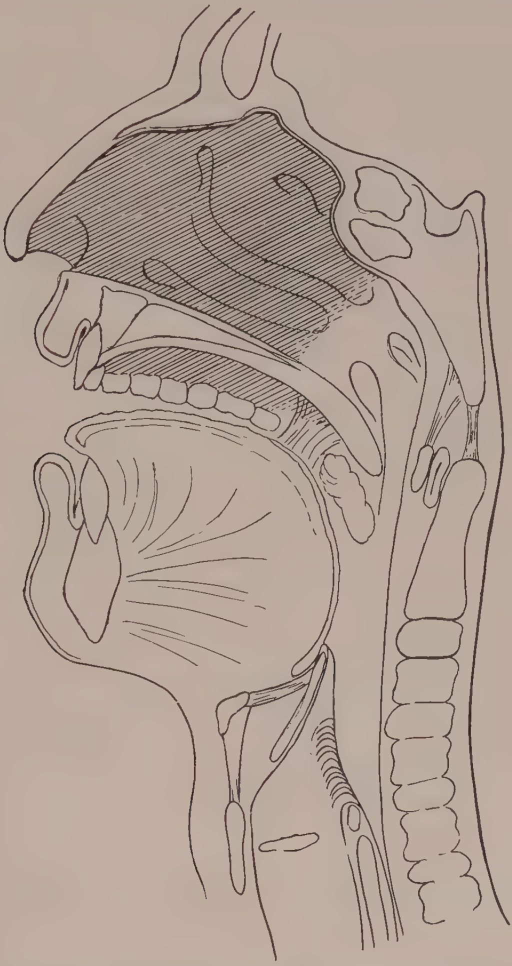

Fig. 205.—Shaded area shows distribution of postoperative anesthesia to touch, pain, and temperature over lateral wall of nasal cavity, hard palate, and anterior part of soft palate on the right, in a case of trifacial neuralgia.

the level of the hard palate above and the pyriform fossa below. Sensation was normal in the nasopharynx and over the epiglottis and the upper aspect of the larynx. There was total paralysis of the right half of the soft palate, and of the right superior, middle, and inferior constrictors of the pharynx.

Examination of a patient who had had section of the posterior root of the right gasserian ganglion for uncomplicated trifacial neuralgia revealed total anesthesia to the tactile, pain, and thermal stimulation over the cutaneous distribution of the right trigeminal nerve, the mucous membrane of the right half of the nose as far back as the posterior choanae, the mucous membrane of the right half of the buccal cavity anterior to a plane passed transversely through points just anterior to the glossopalatine folds. There was a tongue-shaped area along the middle third of the right lateral margin of the tongue in continuity with the region of normal sensibility where sensation was preserved.

Glossopharyngeal neuralgia is a definite clinical entity differing only from trifacial neuralgia in the area of distribution of pain. Treatment must lie along lines similar to those followed in the treatment of trifacial neuralgia.

A CASE OF RECKLINGHAUSEN'S DISEASE WITH INVOLVEMENT OF THE PERIPHERAL OPTIC NERVES AND SPINAL CORD*

HARRY L. PARKER

The most usual form of Recklinghausen's disease is that involving cutaneous structures and peripheral nerves. Less often the multiple tumors, which may be of widely different nature, may be found inside the spinal canal and cranium. Cases have been recorded in which the tumors were gliomas, fibromas, myxomas, osteomas, and endotheliomas. The growths inside the spinal canal and cranium may be associated with very slight changes in the skin and peripheral nerves. In the case described the patient had a combination of neurofibromas on the peripheral nerves and endotheliomas in the orbit and spinal canal.

REPORT OF CASE

Case A311349. Mr. B. P., aged twenty years, came to the Clinic, April 8, 1920. He complained chiefly of a bulging of his left eye with disturbed vision, weakness in his left hand, and difficulty in walking. Numerous nodules were felt on the peripheral nerves and a solitary, fawn colored, café-au-lait patch was noted on the skin just under his left nipple. He had a paralysis of the ulnar nerve in the left hand due to a nodule growing on the nerve and a drop foot on the right due to a similar growth on the right external popliteal nerve. There was evidence of compression of the spinal cord at the tenth dorsal segment. He had a choked disc in the left eye with a vision of 6/30.

The patient was operated on and an endothelioma was removed from his right orbit. Since the tumor had surrounded the optic nerve, this also was removed. The eye-ball was preserved. Later, laminectomy was performed and a tumor was removed from the spinal canal where it was seen to have arisen from the dura mater. It was also an endothelioma. Two nodules on the peripheral nerve were resected and histologically were proved to be neurofibromas.

Although sight was necessarily lost in the right eye, the patient's gait was much improved and there was a general improvement in his functional ability. Fourteen months after operation he reported himself to be enjoying good health and leading an active existence in spite of his disabilities.

The case was chiefly interesting from the point of view of the vulnerable position of the tumors in the central nervous system and the slight manifestation of cutaneous disease. The histologic difference between the tumors on the body surface and inside the orbit and spinal canal was a point also worth recording.

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* Abstract of paper published in full in the Journal of Nervous and Mental Diseases, 1922, lvi, 441–452. From the Section on Neurology, Mayo Clinic.

DIAGNOSIS OF TUMORS OF THE CAUDA EQUINA, CONUS AND EPICONUS MEDULLARIS: REPORT OF EIGHT CASES*

HARRY L. PARKER

Thirty-three patients with spinal cord tumors were observed in the Mayo Clinic from January 1, 1916, to January 1, 1922; in only eight the lesion was situated in the lower spinal segments and the cauda equina. These patients were operated on so that the location of the tumor and the pathologic condition were made manifest. The tumors were intramedullary in two patients and confined to the conus and epiconus; in the remaining six the tumors were either extramedullary and pressing on the conus or infiltrating the cauda equina and spinal cord.

The pathology of the tumors varied from a secondary carcinoma in one patient and endothelioma in another to gliomas in five patients. The pathologic condition in one patient was not ascertained. In three patients so-called ependymal-cell gliomas were present.

The diagnosis in most of the patients was made on few signs, but all gave a very definite history of long continued pain of a peculiar but definite type. The pain was largely nocturnal and relieved by walking and exercise, while it was initiated or increased by rest in bed. The patients preferred to walk the floor at night, or when unable to do so, spent the night sitting up in a chair. Signs of irritation of the cord or roots appeared many months before signs of actual destruction. The pain may be felt in the lumbar spine and sacrum, and be increased on jarring the spinal column, coughing, or sneezing. It may also be felt over the distribution of the caudal roots in a diffuse area or may be confined to one or more sharply localized areas in the lower extremities. On the whole intramedullary tumors produce pain that is localized to small areas, while caudal tumors produce a more diffusely distributed pain.

Seven patients had muscular weakness varying from a complete flaccid paraplegia to a weakness of one group of muscles in one extremity. In the absence of pain this seemed of little importance; in one patient muscular weakness was not present at the time of examination.

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* Abstract of paper published in full in the American Journal of Medical Sciences, 1922, clxiii, 342–364. Copyright by Lea & Febiger, Philadelphia. From the Section on Neurology, Mayo Clinic.

Some disturbance of bowel and bladder control was present in five patients; it was an early symptom in three, but was associated in each case with sensory disturbances around the anus or over a wider area. Sphincter control was retained in three of the patients and even associated with other marked signs of widespread involvement of the cord and roots. Control of micturition and defecation may be retained, therefore, in the presence of definite destruction of the cord and cauda equina, the lowest segments of the conus escaping.

All of the thirty-three patients had some disturbances of sensation which may be slight or severe. It does not, however, bear any relation in its extent to the size of the tumor. A relatively large tumor may be accompanied by but little sensory change. This disturbance of sensation is very important and should always be searched for, especially in the perianal area. It is seldom absent when the sphincteric control is involved.

The tendinous reflexes in all tumors of the cauda equina, conus, and epiconus are either reduced or absent. The disturbance of the cutaneous reflexes is of some importance in the localization of the tumor. Exaggeration of reflexes would necessarily mean involvement of the cord at a point higher than the area under discussion.

Spinal puncture is an aid to diagnosis never to be neglected. In expert hands, failure to obtain fluid is of great importance; also, a yellow fluid with the other characteristics of the Froin syndrome would suggest a disturbance of circulation of the spinal fluid. Roentgen-ray examination is of little value, except as a process of exclusion.

The differential diagnosis of these tumors is a difficult procedure. Inflammation of the peripheral nerves, joint structures, and the cauda equina itself must be considered. The type of pain in tumors is of some assistance, although neuritis of the cauda equina may simulate a tumor almost exactly. Myelodysplasia and congenital anomalies confuse the diagnosis, and hypertrophic arthritis with radicular irritation is at times difficult to distinguish from a growing tumor. Syphilis and tuberculosis of the bone, joints and membranes affecting the cords and its roots secondarily have to be considered, and tumors not in the spinal canal but affecting the sacral roots on their exit into the pelvis, have to be excluded by careful rectal examination.

The course of the disease may be long, eight years being the longest of this series, and actual signs of destruction may not appear until late. Physical signs may be few in comparison to the size of the tumor and the extent of involvement found at operation or necropsy, and so prognosis cannot be accurately determined until exploration shows how extensive is involvement by the tumor.

In a well advanced case diagnosis is easy, but during the comparatively long period antecedent to the appearance of physical signs it is very difficult. At that time, however, the diagnosis may be made on a type of pain, its persistence and secondary factors, as rigidity of the spine and the spinal fluid findings. To tell the exact location of the tumor in the spinal canal is either impossible or very difficult, and it is often a matter of mere speculation before exploration, whether it be in the cord itself, around the caudal roots, or outside the dura mater.

DISTURBANCES OF THE RESPIRATORY RHYTHM IN CHILDREN: A SEQUELA TO EPIDEMIC ENCEPHALITIS*

HARRY L. PARKER

The characteristics of epidemic encephalitis in the children studied were shown by insomnia and changes in character. The insomnia was at times very persistent and the patients slept a few hours in the day and talked, sang, and whistled all night. They became disobedient, impulsive, and emotionally unstable, whereas, before they had been well behaved. Seven children examined in the Mayo Clinic during the past year had these characteristics, but in addition there was a marked disturbance of the respiratory function.

In three cases there was noisy forcible breathing associated with breath holding. The patients stood up, inflated the lungs to the fullest extent and with head flung back held the breath for 15 to 30 seconds. They then released the breath in a doubled up posture and in a position best suited to complete expiration, the breath being released in a series of noisy grunts. Two of the patients held their breath but waved their hands in the air during the process and jumped up and down. One patient, a girl of twenty, was unable to breathe comfortably standing up. She became extremely dyspneic when she stood or walked, and it was impossible for her to run or make any active movements. In the recumbent posture she was perfectly at her ease. Her pulse, which varied accordingly, was about 75 while she was lying down and became uncountable while she stood erect. The remaining two patients had constant noisy respiration, in one case associated with breath holding and petit mal attacks. This latter patient had constant, noisy, puffing respiration without any other respiratory phenomena.

Seven of the eight patients date the onset of their trouble from the first three months of 1920. In five there was a definite history of influenza or epidemic encephalitis and in two a history of some febrile disease, such as measles or tonsillitis. In all these patients treatment was very unsatisfactory.

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The literature on the subject contains some reference to respiratory disturbances in epidemic encephalitis. Hiccuping, yawning, sighing, sobbing, and uncontrollable laughing were met with rather often during the epidemic. Six of the series of eighty-one recorded cases of Hap and Blackfan had marked hyperpnea during the acute stage which disappeared during convalescence. Aaronson and Hass reported cases of children having uncontrollable and persistent hyperpnea some time after onset, and in the latter's case this was associated with breath holding and unconsciousness. Tracings of simple bilateral myoclonic twitchings of the accessory muscles of respiration showed, in a few cases of Hamill, a relation to the respiratory rhythm. The epidemic hiccup was at times severe enough to pull the patient's body into fantastic and awkward positions and it affected not only the diaphragm but also other muscles of the body far away from it.

The anatomic localization of the disease producing such complex syndromes is uncertain. In the simpler types of hiccup and hyperpnea it is probably in the medulla or basal ganglia. The cases of paroxysmal disturbances of repiration probably belong to the myoclonic group of encephalitis and seem to persist for months after onset.

The differential diagnosis from hysteria rests on the comparatively uncommon appearance of hysteria in children and the occurrence of such a disease in as many as seven children during a relatively short time, all dating the onset of their disease from a period when the epidemic was active and in each case associated with an initial febrile episode which in three was definitely encephalitic. The persistence of the symptoms and the similarity of the disease were not more striking than the bizarre and fantastic nature of the disease itself. The combination of insomnia, metamorphosis of character, and disturbance of the respiratory rhythm is a syndrome that has to be added to the polymorphic and kaleidoscopic picture of epidemic encephalitis.

THE INTRANEURAL PLEXUS OF FASCICULI AND FIBERS IN THE SCIATIC NERVE*

J. CHARNLEY McKINLEY

During the past fifteen years various writers have developed the conception of fiber tracts within peripheral nerves analogous to those in the brain and spinal cord. That is, in a given nerve, the fibers that supply a certain muscle or a certain area of the skin have been thought to be situated constantly within a definite region of the nerve trunk at a given level. Various rules of operative procedure in nerve suture, transplantation, and the like have been proposed on the basis of this theory. Previously investigation has been largely by clinical observation and gross dissection. In the present work the problem of functional localization of fasciculi was studied by three methods:

1. The sciatic nerve of an adult human being was dissected from the sacral plexus to the middle of the leg with all its branches, embedded in paraffin in successive blocks and cut serially so that the fasciculi could be traced through serial sections. It was evident that the tibial and common peroneal divisions of the sciatic nerve are great plexuses of anastomosing fasciculi throughout their whole lengths.

2. In a number of dogs the sciatic nerve was partially divided through various segments at the level between the ischial tuberosity and the greater trochanter of the femur, the dogs were killed after fourteen days and the nerves with their branches were stained according to Marchi's method for the demonstration of degenerating myelin sheaths. Degenerations were observed in many of the respective branches of the tibial and common peroneal nerves instead of in one or two of them, showing that there is a definite mixing of the fibers throughout their course down the nerves.

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3. The tendons around the ankle of an anesthetized dog were dissected out and each connected by a string to its respective lever, playing on a drum of smoked paper. The sciatic was then divided between the ischial tuberosity and the greater trochanter of the femur, and the distal stump was stimulated electrically with the minimal current that would produce a contraction. The nerve was split lengthwise into as fine segments as possible for a distance of one centimeter and each segment was stimulated in turn, a tracing of the muscles contracting being obtained with each stimulation. With the exception of two segments, in each of which stimulation produced a contraction of only two muscles, all the muscles supplied by the tibial or common peroneal nerve contracted for every segment stimulated.

Hence, it is impossible to conceive of any functional significance of fasciculi in peripheral nerves.

In case of a transverse lesion of a nerve the operation consists in resecting the scar tissue, the neuroma of the central stump, and the glioma of the peripheral stump until the normal nerve fasciculi of the one and the atrophied bundles of the other are distinctly visible. In the average operation two, three, or more centimeters of the nerve must be resected. It is then advisable to suture the divided ends without torsion in as nearly their normal anatomic relationships as possible. It has been said, "It is indispensable that in their sutures the surgeons appose as exactly as possible the sectioned ends of the various divided nerve fasciculi of the superior end with the same fasciculi of the inferior end." In this study it has been shown that within two centimeters of the length of the sciatic trunk at a point specially studied, there are twenty-three fusions and fifteen divisions of the various bundles and a reduction of eight fasciculi. Thus, after resection of the glioma and neuroma, the fasciculi in the proximal stump cannot correspond to those of the peripheral stump, and the impossibility of following to the letter the above directions is at once apparent.

THE PHENOMENA OF RAYNAUD'S DISEASE*

J. ARTHUR BUCHANAN

In 1862 Raynaud reported a series of cases which presented very unusual features on the part of the vascular apparatus. The local manifestations of Raynaud's disease can be grouped under changes in (1) color and nutrition, (2) sensation, (3) the motor system, and (4) the bones.

The changes in color may be discussed under four main divisions, white, blue, red, and black. The term "local syncope" was introduced by Raynaud to signify the sudden blanching of a part of the body. The affected part suddenly becomes white and cold, and the condition may last for from a few minutes to several hours. Gangrene may supervene.

The term "local asphyxia" denotes the second stage, or periodic attacks of blueness in various parts. This disappears on pressure, with an abnormally long interval before the return of normal or of the bluish coloration. Often the affected part swells temporarily or sweats, making the part cold and clammy. If this asphyxia persists, false edema may result. Local asphyxia and local syncope may succeed one another rapidly and may appear as constantly interchanging processes. This has been spoken of as vasomotor ataxia. Local asphyxia, like local syncope, is paroxysmal, recurrent, and may be symmetric or nonsymmetric. It is more painful than syncope. Desquamation may follow an attack.

Red discoloration is designated by the term "local hyperemia." It has never been observed alone, but follows either syncope or asphyxia. The part is bright red, usually with palpably increased arterial pulsations, increased warmth and moisture of the part, and at times an unpleasant sensation approaching pain, which is usually described as tingling.

The presence of a blackish discoloration has been called spontaneous gangrene. It usually affects the peripheral parts and is of a dry type with clear demarcation from the normal tissue. This may continue for months before sloughing occurs. The gangrene is usually symmetrical and the affected parts heal with a peculiar tapering deformity which is quite striking. Gangrene may appear as slight ulceration or may be massive, involving even a leg with a portion of the thigh.

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* Abstract of paper published in full in the American Journal of Medical Sciences, 1922, clxiv, 14–29. Copyright by Lea & Febiger, Philadelphia. From the Section on Medicine and Neurology, Mayo Clinic.

Pain is almost a constant finding. It may be sharp and paroxysmal, coinciding with the manifestations of syncopal and cyanotic attacks or a painful numbness followed by a sensation of burning and shooting. It radiates to every limb and is increased by pressure.

Sensations of heat and cold are not changed. At times there is a slight diminution of tactile sensation. Burning, tingling, pricking, or a combination of peculiar sensations may be present. Motor disturbances, as clumsiness and slowness in performing ordinary work, are commonly present.

Cassirer described atrophic changes in the bones, the cortex being thinned, with a consequent increase of the marrow space and sharpening of the outline of the canalicular systems.

The author studied the histories of sixty-seven patients observed in the Mayo Clinic. The majority were twenty to fifty years of age. About sixty per cent were females. Sixty-three were born in North America. The birthplaces and the places of residence were so diversified as evidently to have no weight as etiologic factors.

A patient may have Raynaud's disease for many years with more or less good general health. Of fifty patients traced, nine showed no change, eight were worse, and five were dead. The remainder had improved, were entirely well, or their general health was good.

Almost 90 per cent of the patients described the onset as sudden. In one case it followed diphtheria, in another an attack of unexplained jaundice, and in one the condition became aggravated after an attack of influenza. In the others it was impossible to determine what might have been a causal factor. The disturbance apparently does not depend on a toxic process.

The author discusses the changes in color, the sensory symptoms, and the distribution of the gangrene in this series of sixty-seven patients. He also studied the blood pressure, blood picture, pulse rate, and the urine, but found nothing significant. All the patients had negative Wassermann reactions and the histories were negative for syphilis.

Five patients were relieved by warmth, one by cold applications, and one by Blaud's pills. Bier's hyperemia, elevation of the part, the use of thyroid extract, and the eradication of foci did not produce benefit. A warm nonvariable climate seemed to be the only factor to afford relief. Some were able to lessen their attacks by wearing woolens and protecting themselves from the cold as much as possible.

For the better understanding of the particular phase of the disease discussed, the author suggests that the term Raynaud's disease should be discarded in favor of "local syncope of Raynaud," "local asphyxia of Raynaud," and "gangrene of Raynaud." When all three phases of the condition are present the "phenomena of Raynaud" would be a satisfactory substitute.

VIII

ORGANIC AND PHYSIOLOGIC CHEMISTRY

THE PREPARATION OF CERTAIN DERIVATIVES OF CYCLOHEXANE*

ARNOLD E. OSTERBERG AND EDWARD C. KENDALL

Many methods for the preparation of cyclohexane derivatives have previously been employed. The method described herewith for the preparation of cyclohexane and cyclohexanol, embodying Ipatiew's principle of high pressure, offers a simple procedure for the manufacture of these materials on a large laboratory scale with easily accessible materials.

The substance to be reduced, together with a metal oxid catalyst, is placed in a suitably constructed bomb which can be filled at intervals with hydrogen under pressure of 115 to 120 atmospheres, and the whole subjected to a temperature of approximately 250 until reduction is complete. The higher temperature and pressure tend to counteract the decreased activity of a partially poisoned catalyst. The process requires very little attention other than periodic filling and emptying of the bomb. The reaction proceeds to completion with a catalyst much less reactive than that necessary to obtain any reduction by the Sabatier method. The high pressure needed is obtained by use of commercial hydrogen sold in tanks at a pressure of 1,800 pounds for each square inch. Without materially slowing up the reaction the hydrogen tanks may be used without replacement until the pressure is decreased to approximately 1,000 pounds.

During the past year in connection with work on the production of hydroheterocyclic compounds it was necessary to prepare considerable quantities of cyclohexane, cyclohexanol, and some of their derivatives. These are not procurable on the market, although the first two mentioned have been articles of commerce.

In seeking a method which could be standardized for the preparation of cyclohexane and cyclohexanol we have used that of Ipatiew, for reasons given above. By this process about 30 kg. of hexahydrophenol have been prepared, the method being found very satisfactory. Nothing new is offered in the preparation of these compounds, but as they are the necessary starting materials for the production of a series of new substances, the procedure found most satisfactory for the preparation of cyclohexane, cyclohexanol, cyclohexylamine, cyclohexene, and the more simple, well-known members of this series will be outlined, since even after a careful perusal of the literature one is in doubt as to which method to follow.

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A study of orthodisubstituted derivatives of cyclohexane offers many opportunities in determining the effects of one group on the activity of the other, since these compounds lie intermediate to aliphatic and aromatic substances. Studies of orthodisubstituted derivatives of the cyclohexane series are relatively few and these are confined mainly to compounds in which the groups are similar, such as the dibromo and dichloro derivative prepared from cyclohexene. A few compounds in which the *ortho* groups are dissimilar have brief mention in the literature, for example, ortho-iodochloro-cyclohexane,[9, 10] ortho-iodo-cyclohexanol,[8] ortho-iodobromo-cyclohexane, and ortho-cyano-iodo-cyclohexane.[11] In addition, the preparation of ortho-amino-cyclohexanol, ortho-chloro-cyclohexylamine, and ortho-bromo-cyclohexylamine, together with some of their derivatives, will be described.

EXPERIMENTAL

Preparation of catalyst.—Metallic nickel was used almost exclusively. Pure nickel nitrate is calcined at a dull red heat for an hour, cooled, and very finely ground. It may be heated again to a red heat to insure complete decomposition of the nitrate. The powdered nickel oxid is then reduced in a stream of hydrogen at 250 C. for several hours. It is allowed to cool overnight in an atmosphere of hydrogen and is placed in a tightly stoppered flask until used. This catalyst used in the proportion of one part catalyst to ten parts of substance remains in an active state for five or six reductions. If the reduction is proceeding too slowly it is best to replace the old by fresh unused nickel.

Cyclohexane.—Three hundred grams of purified benzene free from thiophene by the isatin test and 30 gm. of nickel catalyst are placed in the bomb and shaken well to obtain a good distribution of the nickel. The bomb is placed in an electrically heated hot air oven at 250 C. and filled with hydrogen at 1,800 pounds pressure; at intervals of two hours during the day more hydrogen is introduced to replace that which has reacted. At night the bomb is not refilled, but is allowed to remain in the oven. At the end of forty-eight hours the reaction is complete. The bomb is then removed, cooled, and the contents poured into a distilling flask and distilled. The fraction boiling between 80 and 85 is collected and is sufficiently pure for synthetic work. The nickel remaining in the flask is washed back into the bomb with the next run and used again. The yield of cyclohexane is 275 gm. or 85 per cent of the theoretical amount.

Cyclohexanol.—Three hundred grams of redistilled U. S. P. phenol is melted and poured into the bomb with 30 gm. of nickel. The reduction is carried out precisely as given for benzene. When completed the reaction product is fractionated, the fraction boiling at 158 C. at 730 mm., being practically pure cyclohexanol. A small amount of cyclohexane and water is formed and is collected in the lower fraction, boiling between 80 C. and 110 C. If the reduction has not proceeded to completion a fraction boiling above 158 is obtained. This may be returned to the bomb with the next run and the reduction is completed. The nickel is also returned. The yield is 255 gm. or 80 per cent.

Cyclohexanon.—Baeyer[6] prepared this substance by the oxidation of cyclohexanol with Beckman's chromic acid mixture and proved its identity with the ketohexamethylene obtained by Perkin, from calcium pimelate. Baeyer used a proportion of 2 gm. of cyclohexanol to 27 gm. of the chromic acid mixture. The method used by us is essentially the same, modified slightly to keep the volumes down when dealing with 100-gm. portions.

One hundred grams of cyclohexanol and 150 c.c. of water are placed in a one-liter flask and cooled in ice water. To this is added gradually 35 c.c. of concentrated sulfuric acid. One hundred grams of sodium dichromate is dissolved in a solution of 35 c.c. of concentrated sulfuric acid in 150 c.c. of water. The chromic acid solution is added to the cyclohexanol mixture in 10 c.c. portions over a period of two hours, and the solution is shaken well after each addition. To complete the reaction the mixture is heated in a water-bath for two hours, cooled, and ether extracted; the extract is dried with potassium carbonate and the ether distilled off. The cyclohexanone boils constantly at 155 C. The yield is 83 gm. or 85 per cent.

Ortho-chloro-cyclohexanone.—This may be prepared by a method similar to that used by Kotz for the corresponding bromin compound. Chlorin is bubbled through a mixture of 20 gm. of cyclohexanone, 15 gm. of calcium carbonate, and 50 c.c. of water in a flask immersed in cold water, until the reaction is complete. The oil is extracted with ether, dried, and the ether removed. The oil does not distil *in vacuo* without decomposition and is difficult to obtain pure and free from chlorin.

Attempts to form an aminoketone invariably led to condensation products, and secondary and tertiary amins.

Cyclohexanone oxime.—Baeyer[6] obtained the oxim in theoretical yield, by allowing the ketone to react with hydroxylamin hydrochlorid and excess sodium hydrogen carbonate in alcohol at water-bath temperature, extracting the residue with ether, and recrystallizing the residue from petroleum ether. It may also be obtained with equal facility and in theoretical yield in water solution by the following method:

Eight and four-tenths grams of hydroxylamine sulfate in 60 c.c. of water is added in small portions to a mixture of 10 gm. of cyclohexanone and 50 c.c. of water containing 4.1 gm. of sodium hydroxid or excess of bicarbonate. The reaction flask should be continually shaken and cooled under tap water. When nearly all the hydroxylamin has been added, the oxime separates as a crystalline solid and is filtered immediately, washed with water, and dried. If the reaction mixture is not cooled a red color is developed and the yield decreased. The dried product recrystallized from boiling ligroin melts at 88.

Cyclohexylamine.—Many attempts to prepare cyclohexylamin by direct catalytic reduction of anilin have at best resulted in very poor yields. By Paal's method a yield of 10 per cent has been obtained in eighty hours.[37] The use of Sabatier's and Senderens' method results in destruction and numerous side reactions. Ipatiew[19] reports a yield by his method of from 40 to 50 per cent, with nickel oxid as a catalyst and a pressure of 115 to 120 atmospheres. We have attempted to use Ipatiew's method with a nickel catalyst, but it has invariably resulted in such great destruction and production of side reactions as to cause its abandonment.

Cyclohexylamine may be obtained in good yield by reduction of ketohexamethylene oxime by either the method of Sabatier and Senderens or that of Baeyer.[6]

In Baeyer's method 5 gm. of the oxime is dissolved in 200 c.c. of absolute alcohol and added to 25 gm. of sodium. It is best to dissolve all the oxime in a small amount of alcohol, and add the solution to the sodium. Additional alcohol is then poured through the reflux condenser. In this way all the oxime is present during the entire reaction.

Ten grams of cyclohexanone oxime in 30 c.c. of absolute alcohol is added through a reflux condenser to 50 gm. of sodium strips, followed by an additional 400 c.c. of absolute alcohol. When the reaction is complete the alcohol is distilled from a water-bath, water is added, and the solution made acid with hydrochloric acid. The acid solution is evaporated to dryness on a water-bath with the help of an air blast. A small amount of water is added (20 c.c.), and an excess of solid potassium hydroxid. The oil which separates is extracted with ether, dried, and distilled, after removal of the ether; its boiling is 133 C. It distils with some decomposition and takes up carbon dioxid very rapidly, and consequently is best distilled in a stream of hydrogen as Baeyer recommends. However, this is not necessary if the receiver is protected with a soda-lime tube. The melting point of the carbonate is 110 C., the hydrobromid 195 C., the hydrochlorid 204 C., the acetate 147 C., and the acetyl derivative 99 C.

Cyclohexene.—Many methods have been proposed for the production of cyclohexene from cyclohexanol, using various dehydrating agents. It is also frequently made by treating monohalid cyclohexanes with alkalis, such as calcium oxid[33] and quinolin. Among the dehydrating agents may be mentioned particularly oxalic acid,[38] iodin,[17] sulfuric acid,[34] dimethyl sulfate,[15] and potassium hydrogen sulfate.[12]

Zelinsky, using one part of cyclohexanol to five parts of anhydrous oxalic acid at 100 C. to 110 C., obtained cyclohexene. In using this method it has been found that this proportion may be considerably increased and good yields obtained. The process may be made continuous by addition of cyclohexanol, as the tetrahydrobenzene and water distil over, and with occasional addition of anhydrous oxalic acid to replace that which is destroyed or distils over as the ester of cyclohexanol.

The objection to using dimethyl sulfate is of course obvious; calcium oxid requires a temperature of 350 C. and special apparatus, and potassium hydrogen sulfate gives poor yields due to formation of cyclohexyl ether. The catalytic sulfuric acid method described by Senderens is easy of application and gives practically a 90 per cent yield. The procedure followed is precisely that of Senderens.

One hundred grams of cyclohexanol and 2 c.c. of concentrated sulfuric acid are slowly distilled until white fumes are evolved and the odor of sulfur dioxid is apparent. The water and cyclohexene in the distillate are separated, the cyclohexene dried with potassium carbonate, and redistilled. Sixty grams of pure cyclohexene, boiling 82 C. to 84 C., is obtained, and 16 gm. of a higher boiling fraction, consisting of a mixture of unacted-on cyclohexanol and cyclohexene. The yield of pure cyclohexene is 73 per cent. This may be increased to approximately 90 per cent by retreating the higher fraction with the next run.

In searching for other agents which would serve to dehydrate cyclohexanol to cyclohexene, phosphorus trichlorid has been found to be fairly efficient. Its disadvantage lies in the amount of phosphorus trichlorid necessary to be used and in the mechanical losses of cyclohexene which occur. About 1 kg. of cyclohexene has been prepared by the following method:

Two hundred and seventy-four grams of phosphorus trichlorid is added slowly through a dropping funnel to 300 gm. of cyclohexanol in a one-liter flask fitted with a reflux condenser. The temperature is maintained at 70 C. by immersion in a water-bath. Addition of the first mole (137 gm.) of phosphorus trichlorid produces a vigorous reaction, but the second may be added more rapidly. When all the phosphorus trichlorid has been added the product is refluxed for four hours and then distilled from the phosphorus oxid. One hundred and fifty cubic centimeters of water is added to the distillate through a reflux condenser and the mixture is refluxed for a short time to decompose all excess phosphorus trichlorid. The cyclohexene is separated from the aqueous layer, dried, and distilled. The yield of cyclohexene is 65 per cent of the theoretical amount, or 160 gm. of tetrahydrobenzene boiling between 82 C. and 87 C., and 30 gm. of a fraction boiling between 87 C. and 160 C.

It is necessary to have the cyclohexanol warm when the trichlorid is added, as otherwise considerable chloro-cyclohexane is formed, which is not broken down by subsequent treatment and may be obtained in the final distillation as the fraction boiling at 143 C.

Ortho-chloro-cyclohexanol.—This substance, described by Fortey, was made by shaking tetrahydrobenzene with a dilute hypochlorous acid solution, the hypochlorous acid being made by passing chlorin into water containing freshly precipitated mercuric oxid. Fortey described it as a yellowish oil distilling with decomposition and having a characteristic odor. Prepared by the following method it is a water-white oil possessing a characteristic odor, distilling at atmospheric pressure with only slight decomposition:

One hundred cubic centimeters of cyclohexene (about three times the calculated quantity) is shaken with 1,700 to 1,800 c.c. of a 2 per cent hypochlorous acid solution; the acid is added in 200 c.c. portions and the mixture shaken until it is decolorized before the addition of more. When all hypochlorous acid has been added the mixture is shaken until 1 c.c. gives only a faint or no yellow color with potassium iodid solution. The hypochlorous acid has always been made by bubbling carbon dioxid through a suspension of bleaching powder in water and filtering off the calcium carbonate. The reaction product is saturated with salt and steam distilled. The distillate is saturated with salt, and the upper layer of cyclohexene and ortho-chloro-cyclohexanol removed and fractionated. The first fraction boiling below 90 C. at 20 mm. is a mixture of water, unacted-on cyclohexene, and some ortho-chloro-cyclohexanol, which may be used again. The ortho-chloro-cyclohexanol boils at 92 C. under pressure of 10 mm. The yield is 85 gm.

Substance, 0.1236: AgCl, 0.1298.

Calculated for $C_6H_{11}OCl$: Cl, 26.35. Found: 25.99.

Ortho-amino-cyclohexanol.—No mention of ortho-amino-cyclohexanol can be found in the literature, although it is easily prepared from ortho-chloro-cyclohexanol and alcoholic ammonia, the chlorin being substituted by the amino group. In aqueous solutions secondary and tertiary amines are the chief products, but if sufficient strength of alcohol is used to maintain a clear solution the primary amine is the chief product.

For the preparation of the free amine the following has been found to be the best procedure: Twenty-six and eight-tenths grams (½ mole) of ortho-chloro-cyclohexanol is placed in a pressure bottle (the ordinary citrate of magnesia bottle fitted with a rubber stopper which can be clamped down is satisfactory) and 100 c.c. of a strong solution of ammonia in 50 per cent alcohol is added. If the solution is not clear, a higher percentage of alcohol is used. The bottle is shaken well and is then heated in a steam-bath for one hour. The contents of five such bottles after cooling are poured into a one-liter distilling flask, 60 gm. anhydrous sodium carbonate is added, and the alcohol and water distilled off; the temperature should be allowed to rise to 110 C. and maintained there until the greater portion of water is removed. Two hundred cubic centimeters of alcohol is added. The salts are removed by filtering the hot solution with suction, washing the precipitate well with alcohol. The alcohol is removed by distillation and the residue fractionated *in vacuo*, using the side neck of the flask as a condenser and immersing the receiver flask in ice-water.

The fraction distilling up to 120 C. at 7 mm. pressure is redistilled at atmospheric pressure. The pure ortho-amino-cyclohexanol boils at 104 at 7 mm. pressure and at 212 C. at atmospheric pressure. It crystallizes in the receiver in rosets which melt at 65 C. The yield is 70 gm.

Substance, 0.0100: Amino nitrogen, 2.19 c.c. (21° and 734 mm.).

Calculated for $C_6H_{13}ON$: N, 12.17. Found: 12.00.

Melting point of salts made from the corresponding acid and an ether solution of the amine: hydrochlorid, 175 C.; hydro-iodid, 187 C.; hydrobromid, 191 C.; carbonate, 139 C.; sulfate not melted at 250 C.

Ortho-chloro-cyclohexylamine.—In attempting to prepare an *ortho* halogen cyclohexylamine, ortho-amino-cyclohexanol was treated with fuming hydriodic acid in a sealed tube at temperatures from 100 to 150. It was found that the iodin did not replace the hydroxy group at a temperature below 130, while at a higher temperature there was a deep-seated decomposition, with the separation of ammonium iodid. Hydrobromic acid also failed to substitute. Thionyl chlorid does not replace the hydroxy group even when refluxed at the boiling point. Phosphorus trichlorid does not substitute the hydroxy group with chlorin, producing instead an ester of a phosphorus acid. The great resistance of the hydroxy group suggested the necessity of using phosphorus pentachlorid. When this was tried in chloroform a very poor yield of ortho-chloro-cyclohexylamin was obtained. Further investigations showed that phosphorus oxychlorid readily reacts with ortho-amino-cyclohexanol in chloroform even at a temperature of 0 C., apparently forming the phosphoric acid ester. If, however, the hydrochlorid of ortho-amino-cyclohexanol is suspended in chloroform the reaction with phosphorus oxychlorid is practically suppressed. Phosphorus pentachlorid, even at 0 C., reacts vigorously with the hydrochlorid of ortho-amino-cyclohexanol.

The reaction product dissolved in water after the treatment with phosphorus pentachlorid in chloroform is made alkaline with sodium hydroxid, extracted with ether, the ether removed, and the residue consisting of ortho-chloro-cyclohexylamine distilled *in vacuo*. The boiling point is 85 C. at 15 mm. pressure.

Fifty-seven and five-tenths grams (½ mole) of ortho-amino-cyclohexanol is dissolved in 300 c.c. of anhydrous and alcohol-free chloroform. The chloroform solution is placed in a one-liter Erlenmeyer flask, with side neck, and fitted with a one-hole rubber stopper. A few milligrams of methyl orange is added and dry hydrogen chlorid led in through a glass tube until the reaction is distinctly acid, indicating complete formation of the hydrochlorid. The flask is cooled in ice-water. One hundred and fifty grams of phosphorus pentachlorid, ground in a dry mortar to a fine powder, and about 300 c.c. of purified chloroform are placed in a one-quart Mason fruit jar, which is packed in an ice-and-salt mixture. To this suspension, which is stirred mechanically and maintained below 0, is added the mixture of ortho-amino-cyclohexanol hydrochlorid and chloroform. This will require approximately one hour. The solution may then be filtered. The hydrochlorid of the ortho-chloro-cyclohexylamin is quite soluble in chloroform, but a considerable portion will separate at 0. The chloroform solution is placed in a one-liter distilling flask. One hundred cubic centimeters of water is added and the flask placed under a reflux condenser. Occasional shaking will start the reaction, decomposing the phosphorus oxychlorid. After the vigorous reaction has subsided it is refluxed in a water-bath for not less than ninety minutes in order to decompose the last traces of phosphorus oxychlorid. The chloroform is then distilled and the residue placed in a tall jar. The volume of the residue should be between 100 and 200 c.c. This is packed in ice and salt, and a saturated solution of sodium hydroxid in water is added. The solution is stirred with a mechanical stirrer until it becomes very thick. Ether is then added and sufficient sodium hydroxid to make the solution distinctly alkaline. Solid sodium hydroxid is now added, and about 500 to 600 c.c. of ether. The salt separates in solid, dry form and is readily extracted with ether. Three extractions are generally sufficient. The ether is dried over solid sodium hydroxid, removed by distillation, and the ortho-chloro-cyclohexylamin distilled *in vacuo*. The yield depends on the extent to which water is excluded and may reach 70 to 80 per cent. If water is not completely excluded the yield may drop as low as 50 per cent. The ortho-chloro-cyclohexylamin is a colorless oil of characteristic odor which does not solidify at −10.

Substance, 0.1412: AgCl, 0.1510.

Calculated for $C_6H_{12}NCl$: Cl, 26.55. Found: 26.45.

Hydro-anilids from ortho-amino-cyclohexanol and ortho-chloro-cyclo-hexylamine may be quantitatively prepared by the usual methods in an indifferent solvent, such as chloroform. As examples, the preparation of the acetyl and chloro-acetyl derivatives is given.

Acetyl-ortho-chloro-cyclohexylamine, $CH_2CH_2CH_2CH_2CHClCH.NHCOCH_3$.—To 13.4 gm. of ortho-chloro-cyclohexylamine dissolved in 50 c.c. of anhydrous chloroform and immersed in ice-water is added a solution of 12 gm. (one and one-half times the theoretical amount) of acetyl chlorid in chloroform. When all is added the solution is refluxed for about two hours. A small amount of alcohol is added to decompose the excess acetyl chlorid, and the chloroform distilled off on a water-bath. The residue may be recrystallized by dissolving it in 90 per cent alcohol and diluting this solution with water; the melting point is 88 C.

Chloro-acetyl-ortho-chloro-cyclohexylamine, $CH_2CH_2CH_2CH_2CHClCH.NH.CO.CH_2Cl$.—This is prepared by a procedure identical with that given for the acetyl, using one and one-half times the calculated amount of chloro-acetyl chlorid. It is recrystallized from the alcohol by the addition of water. It is soluble in hot water, one part in 220; in cold water, one part in 2,000. The chloro-acetyl-ortho-chloro-cyclohexylamin melts at 111.

Substance, 0.0882: AgCl, 0.1192.

Calculated for $C_8H_{13}ONCl_2$: Cl, 33.76. Found: 33.43.

Cyano-acetyl-ortho-chloro-cyclohexylamine, $CH_2CH_2CH_2CH_2CHClCH.NH.CO.CH_2CN$.—The chloro-acetyl-ortho-chloro-cyclohexylamin may be treated with large excesses of sodium cyanid in water at the boiling point for a short time with substitution taking place only on the side chain. The yield, however, is not particularly good, since boiling with alkalis decomposes the nitril present, to some extent.

A mixture of 4 gm. of chloro-acetyl-ortho-chloro-cyclohexylamine and 4 gm. sodium cyanid in 400 c.c. of water is boiled for ten minutes. The solution is then quickly made acid to methyl orange by addition of about 15 c.c. of concentrated hydrochloric acid diluted 1 : 1. The cyano-acetyl-ortho-chloro-cyclohexylamin crystallized on cooling. The yield is 2.3 gm. It may be purified by recrystallizing from hot water; the melting point is 139 C.

Substance, 0.1357: AgCl, 0.0965.

Calculated for $C_9H_{13}ON_2Cl$: Cl, 17.59. Found: 17.59.

Ortho-chloro-hexahydro anilid of malonic acid, $CH_2CH_2CH_2CH_2CHClCH.NH.CO.CH_2COOH$.—This may be obtained by converting the corresponding cyano compound first to the ester, and then hydrolyzing the ester to the sodium salt with an aqueous solution of sodium hydroxid.

Four grams of the cyano-acetyl-ortho-chloro-cyclohexylamine is dissolved in 75 c.c. of alcohol, which is then saturated with dry hydrogen chlorid. It is refluxed for one hour while passing a stream of dry hydrogen chlorid through the solution. The solution is concentrated to one-half the original volume, the ammonium chlorid removed by filtering, and the remainder of the alcohol distilled off *in vacuo.* The residue is taken up in water, 5 c.c. of 30 per cent sodium hydroxid added, and the product shaken until the saponification is complete. The alkaline solution is then acidified with hydrochloric acid and allowed to stand. The free acid crystallizes slowly; the melting point is 132 C.

Substance, 0.1598: AgCl, 0.1046.

Calculated for $C_9H_{14}O_3NCl$: Cl, 16.14. Found: 16.17.

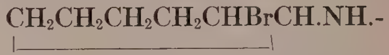
Ortho-bromo-cyclohexylamine, $\underline{CH_2CH_2CH_2CH_2CHBrCH}.NH_2$.—This may be obtained in a manner similar to that given for the ortho-chloro-cyclohexylamine. It is not necessary, however, to maintain as low a temperature during the reaction.

Fifty-seven and one-half grams of ortho-amino-cyclohexanol is precipitated as the hydrochlorid salt in anhydrous chloroform, as described for the preparation of the corresponding chlorin derivative. This suspension is added to a suspension of phosphorus pentabromid in anhydrous chloroform. The phosphorus pentabromid is prepared by adding 70 c.c. of dry bromin to 17 gm. of yellow phosphorus in 150 c.c. of chloroform, cooling the jar in ice-water, and stirring mechanically. During the addition of the ortho-amino-cyclohexanol hydrochlorid it is not necessary to cool the reaction mixture, as the temperature does not rise above 35 C. to 40 C. When the mixture becomes clear the chloroform is removed by distillation on a water-bath. About 300 c.c. of toluene is then added and the solution cooled. The crystals which separate are filtered off, washed well with toluene, and dried.

Purification is effected by dissolving the crystals in a small amount of water, making this solution strongly alkaline with a 30 per cent solution of sodium hydroxid, and extracting this product a few times with toluene. The toluene is dried for not more than one hour over stick sodium hydroxid and the amin is then precipitated as the hydrochlorid salt with hydrogen chlorid, in the form of needles, melting at 168. The yield is 75 gm. or 70 per cent.

Substance, 0.0732: AgHal., 0.1142.

Calculated for $C_6H_{12}NBrCl$: Halogen, 54.04. Found: 53.89.



Acetyl-ortho-bromo-cyclohexylamine, $CH_2CH_2CH_2CH_2CHBrCH.NH.COCH_3$.—To 21.4 gm. of ortho-bromo-cyclohexylamin hydrochlorid in toluene is added 10 c.c. of acetyl chlorid and the mixture is refluxed for several hours. When the reaction is completed the toluene is removed *in vacuo.* The solid residue is dissolved in a small amount of warm alcohol and ice-water added. An oil separates, which crystallizes in a short time. The melting point of the acetyl derivative is 103 C. to 104 C. The yield is 13.5 gm. or 61 per cent.

Substance, 0.1516: AgBr, 0.1312.

Calculated for $C_8H_{14}ONBr$: Br, 36.32. Found: 36.81.

Attempts to prepare ortho-iodo-cyclohexylamin in a manner analogous to the preparation of the chlorin and bromin compounds, using phosphorus tri-iodid in chloroform, were unsuccessful. Invariably the main products were esters of ortho-amino-cyclohexanol.

Substitution of bromin for iodin in ortho-bromo-cyclohexylamine, using potassium iodid in aqueous or alcoholic solution, has given 50 per cent substitution, but the product is too impure for definite identification.

SUMMARY

Methods for obtaining cyclohexane derivatives by direct reduction of the corresponding benzene compounds have been reviewed. The method of Ipatiew for the reduction of benzene and phenol has been particularly applied.

Methods, with some modifications which are most applicable for the laboratory production of cyclohexane, cyclohexanol, cyclohexanone and its oxime, cyclohexylamine, and cyclohexene, are described.

Methods for obtaining the following *ortho* substituted cyclohexane compounds in which the ortho groups are dissimilar, chloro-cyclohexanone, chloro-cyclohexanol, amino-cyclohexanol, chloro-cyclohexylamin and bromo-cyclohexylamin, with certain of their derivatives, are given.

Work in this series is being continued.

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ORTHO-DIETHYLAMINOCYCLOHEXANOL ESTER OF PARA-AMINOBENZOIC ACID*

ARNOLD E. OSTERBERG AND EDWARD C. KENDALL

Amino alcohol esters of aromatic acids are known to possess physiologic properties, chief among which is that of producing local anesthesia.

The anesthetic effect[1] of the diethylamino ethyl ester of para-aminobenzoic acid (procaine) is ascribed in part to the linkage, $-\mathrm{O}-\overset{H_2}{\mathrm{C}}-\overset{H_2}{\mathrm{C}}-\mathrm{N}=$, the maximum being produced when the oxygen is bound directly to the carbonyl of an aromatic acid.

Cyclohexanol resembles more definitely an aliphatic alcohol than an aromatic phenol. Similarly the properties of ortho-aminocyclohexanol are those of an aliphatic amino alcohol. In discussing the properties of this substance with Professor Julius Steiglitz he suggested the possibility of its use in the preparation of esters of the above type.

With the idea of maintaining those linkages to which physiological action is ascribed, but at the same time materially enhancing its molecular weight, we have prepared a homologue of procaine, the ortho-diethylaminocyclohexanol ester of para-aminobenzoic acid. The physiological properties of this compound together with those of derivatives of this ester containing substituents in the cyclohexane ring are being studied and will be reported elsewhere. This report concerns only the synthesis of the ortho-diethylaminocyclohexanol ester of para-aminobenzoic acid.

PREPARATION OF ORTHO-DIETHYLAMINOCYCLOHEXANOL

Fifty-four grams of ortho-chlorcyclohexanol is treated with twice the theoretical amount of diethylamine at 150 C. in a sealed tube for several hours. To the reaction product is added 25 gm. of sodium carbonate and a small amount of water, and the excess diethylamine and water boiled off. The residue is extracted with absolute alcohol. After removal of

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the alcohol the ortho-diethylaminocyclohexanol is dissolved in dilute hydrochloric acid and steam distilled to remove any unchanged ortho-chlorcyclohexanol. The residue is then made strongly alkaline and again is steam distilled. The amin separates in the distillate as a clear oil. It is removed by ether extraction, dried, and fractionated *in vacuo.* The fraction boiling at 100 to 150 C. at 10 mm. is redistilled at atmospheric pressure.

Boiling point 224 at 730 mm.

The hydrochlorid formed from the amin in ether and hydrogen chlorid melts at 160.

Substance 0.2518 gm.	Cl. 0.0428 gm.	
0.2040 gm.	N. 0.0143 gm.	
Calculated for $C_{10}H_{22}ONCl$	Cl. 17.07 per cent.	Found: 17.01 per cent.
	N. 6.75 per cent.	Found: 7.00 per cent.

ORTHO-DIETHYLAMINOCYCLOHEXANOL ESTER OF PARA-NITROBENZOIC ACID

Seventeen grams of ortho-diethylaminocyclohexanol is added gradually to a solution of 20 gm. of para-nitrobenzoyl chlorid in absolute ether. The reaction proceeds easily, but the mixture is allowed to stand for a few hours to insure completion.

The hydrochlorid of the ortho-diethylaminocyclohexanol ester of para-nitrobenzoic acid separates as a pasty mass, and is filtered off. The yield corresponds to 80 per cent of the calculated amount. The hydrochlorid melts at 175.

Substance 0.3550 gm.	Cl. 0.0345 gm.	
0.1810 gm.	N. 0.0140 gm.	
Calculated for $C_{17}H_{25}O_4N_2Cl$	Cl. 9.94 per cent.	Found: 9.72 per cent.
	N. 7.85 per cent.	Found: 7.73 per cent.

ORTHO-DIETHYLAMINOCYCLOHEXANOL ESTER OF PARA-AMINOBENZOIC ACID

Excess tin is added to a suspension of the hydrochlorid of the ortho-diethylaminocyclohexanol ester of para-nitrobenzoic acid in strong hydrochloric acid. During the reduction the temperature is maintained at about 35 until the reaction is complete. The solution is then diluted and the tin removed with hydrogen sulphid.

Excess sodium hydroxid is added to the clear filtrate and the resulting oil extracted with ether. The ether solution is dried and the ether removed by distillation.

The residue of the ortho-diethylaminocyclohexanol ester of para-aminobenzoic acid crystallizes slowly and is obtained as wide plates; the melting point is 72 with preliminary softening.

Substance, 0.1512 gm. N. 0.0147 gm.
Calculated for $C_{17}H_{26}O_2N_2$ N. 9.65 per cent. Found: 9.72 per cent.

The monohydrochlorid melts at 163.

SUMMARY

A homologue of procain, the ortho-diethylaminocyclohexanol ester of para-aminobenzoic acid has been prepared.

The physiologic action of this substance and derivatives containing substituents in the cyclohexane ring are being studied.

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THE RELATION OF CHEMICAL STRUCTURE TO PHYSIOLOGIC ACTION OF CERTAIN SUBSTITUTE PHENYL CARBINOLS AND RELATED COMPOUNDS*

J. PAUL QUIGLEY

The purpose of this thesis was to determine whether substitutions for the inactive hydrogens of the CH_2OH group in aromatic compounds affect the properties of these substances as local anesthetics.

A series of compounds chemically related to benzyl alcohol were synthesized and an investigation made of some of their physiologic properties. The compounds so considered were methyl phenyl carbinol, diethyl ortho-oxyphenyl carbinol, trichlormethyl phenyl carbinol, diphenyl carbinol, dibenzyl phenyl carbinol and hydrobenzoin acetate.

With the exception of methyl phenyl carbinol and dibenzyl phenyl carbinol a determination was made of the effect of these substances when applied to the frog's sciatic nerve. Determinations were also made with certain of these compounds as to their effect on local sensation in man, both on mucous membrane and following subcutaneous injection, their action following subcutaneous injection in animals, their toxicity under these conditions and the effect of intravenous injections on the blood pressure and respiration of animals.

In several cases the compounds investigated were found to possess a narcotic effect or local anesthetic action, but none of these actions are considered to be of practical importance.

The presence of the inactive hydrogens of the carbinol group appear to be of importance for the production of the local anesthetic action of the phenyl carbinols.

Substitution for one inactive hydrogen lessened the local anesthetic action. Substitution for both inactive hydrogens usually abolished or very greatly diminished the local anesthetic action.

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science, 1921. From the Department of Pharmacology, University of Minnesota, Minneapolis.

Alterations in the side chain of certain of the aromatic carbinols do not appear to agree exactly with similar modifications in the structure of aliphatic carbinols.

Incidentally it was found that the intravenous injection of moderate doses (up to 10 mils) of a 10 per cent emulsion of olive oil was practically without effect on the blood pressure and respiration of dogs and cats.

THE DISTRIBUTION OF CALCIUM IN THE TISSUES WITH SPECIAL REFERENCE TO SMOOTH AND STRIATED MUSCLE*

CHARLES E. SHEPARD

Although chemical analysis of the ash of tissue has long been under investigation, there is a striking paucity in data of quantitative value. Berzelius, in the first decade of the nineteenth century, described the importance of the relation between chemical constituents of tissues and their physiologic response. Von Liebig and his students undertook the first systematic chemical studies of the elements present in the ash of various tissues including blood and lymph. Their work has been duplicated but their results by no means confirmed by later investigations, chief among which are those of Bunge,[2, 3] and Katz, and more recently of Saiki, Costantino, and Meigs and Ryan. The extreme variation in the figures denoting proportion of element in tissue obtained by these several workers indicates the necessity for considering more carefully the various important sources of error which must be dealt with in such analyses. The introduction by Neumann of more suitable methods of ashing and more accurate inorganic quantitative methods, and the employment of the electric oven in the former process, have decreased the amount of variability somewhat, but we are still in need of more accurate methods and a stricter observance of chemical and morphologic sources of error before we can hope for results of true quantitative value.

With the object of eliminating as far as possible the sources of error in the present work, I have undertaken a careful study of the various factors which may have contributed to the inaccuracy of previous results.

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* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science, 1922. From the Department of Physiology, University of Minnesota, Minneapolis.

CHEMICAL ANALYSIS

Loss of material by crude ashing processes was early recognized as an important source of error. But a satisfactory method was not offered until the adoption of Neumann's process, and the utilization of the electric oven. I have found the latter most satisfactory for the present work and after using both methods in the ashing of substances of known calcium content, have adopted it as being fully as accurate.

Analytic work which is to be of true quantitative value must be preceded by a careful study of the comparative merits of the various methods and adoption of the most accurate. A comprehensive review of the various tests for calcium is given by Clark. After trial of several methods, the volumetric test used by Neumann, Treadwell, Kramer and Howland, Halverson and Bergeim, McClendon, McCrudden, and others was adopted.

MORPHOLOGIC ANALYSIS

A common source of error in previous work has been the disregard for individual variation in tissues of animals of the same species. The tissue constituents have been found in the present work to vary in the same animal under different nutritional conditions and in different animals of the same species under similar nutritional conditions. Therefore, even moderate accuracy can be attained in analyses only by accepting that figure which represents the average of a large series of analyses on the same species of animal under similar nutritional conditions. In the present investigation the accepted figure is the average of a series of analyses on the same tissues from twenty-five dogs which were in similar conditions of nutrition, the tissues removed and analyzed by the same technic. A shorter series was run on the same tissues of rabbits and cats.

Results of analyses have usually been expressed as the amount of element present in a known weight of the fresh tissue. However, there has been a most unrestricted employment of the term "fresh" tissue. Since drying begins the moment the tissue is displaced from its natural environment, there is a gradient change in its weight, so that any figure which represents the proportion of element in the whole tissue must vary with the length of time elapsing between removal of the tissue and its weighing. Earlier workers have not attempted in any way to limit this error. Meigs and Ryan define fresh tissue as that which still shows response to a stimulus. But even this is a broad statement when accurate calculations are desired. The necessity for a stricter observance of the term "fresh" tissue is obvious. In the present work rapid technic of removal, and the fact that tissues so removed were immediately placed in air-tight weighing bottles, minimized this error.

By far the most important source of error in the analysis of tissue is the error due to the difficulty in obtaining "pure" tissue. Muscle tissue, for example, is always contaminated by the presence of connective tissue, blood, and lymph. Attempts to eliminate this important factor have so far been unsuccessful. In the present work a new method has been utilized which greatly minimizes the error.

PROCEDURE IN EXPERIMENTATION

It was considered wise to limit the scope of the present work to the study of a single element. Calcium was chosen partly because of the extreme variation in figures for this element particularly, as obtained by previous investigators. Also for the sake of future experimental work it was desired to learn the normal calcium content of the muscle tissue. Very little has so far been learned concerning the amount of elements contained in different tissues of one and the same animal. This has been undertaken in the present work.

Adult male animals were used in every case. To insure a normal calcium balance (Voorhoeve) no food was given to animals seventy-two hours previous to the experiment. Dogs 6, 10, and 16 (Table 1) show the effect of only one day of starvation. Tissues used were the sartorius (striated), which can be quickly excised, the muscular sheet from the pyloric region of the stomach (smooth), which was removed rapidly by a modified Rammstedt technic, and the retractor penis muscle (mixed). Samples of blood and plasma were taken from the same animal and also Achilles' tendon as an example of pure connective tissue. Small pieces of the muscle tissue were taken for sectioning at the same time. Tissues were weighed, ashed, and the calcium content of the ash calculated as per cent of the whole tissue (Table 1). Serial sections were made, stained with Mallory's connective tissue stain, and placed under the Edinger projection apparatus. The outlines of the areas occupied by contaminating tissue were mapped out on American Linen Record paper which has been found of very uniform weight. The areas representing contaminating tissue were cut out and weighed and the proportion to the whole determined, as has been done by Hammar and

TABLE 1

Summary of Calcium Content of Blood and Tissues (Grams of Element in 100 Gm.)

Dog.	Blood.	Blood.	Plasma.	Plasma.	Stomach.	Retractor.	Sartorius.	Tendon.
6*	0.0082	......	0.0187	......	0.0210	0.0260	0.0342	0.0194
7	0.0064	......	0.0139	......	0.0180	0.0208	0.0327	0.0184
8	0.0059	......	0.0139	......	0.0148	0.0239	0.0294	0.0170
9	0.0060	......	0.0138	......	0.0142	0.0250	0.0309	0.0168
10*	0.0080	......	0.0178	......	0.0210	0.0277	0.0346	0.0196
11	0.0063	......	0.0141	......	0.0190	0.0256	0.0328	0.0184
12	0.0060	......	0.0139	......	0.0144	0.0244	0.0335	0.0180
13	0.0063	......	0.0138	......	0.0147	0.0254	0.0319	0.0173
14	0.0064	......	0.0140	......	0.0205	0.0266	0.0314	0.0200
15	0.0061	......	0.0137	......	0.0175	0.0265	0.0291	0.0186
16*	0.0082	......	0.0188	......	0.0240	0.0290	0.0354	0.0196
17	0.0064	0.0066	0.0140	0.0146	0.0180	0.0281	0.0366	0.0184
18	0.0063	0.0065	0.0137	0.0139	0.0165	0.0250	0.0342	0.0176
19	0.0062	0.0060	0.0142	0.0139	0.0154	0.0187	0.0284	0.0174
20	0.0074	0.0073	0.0147	0.0146	0.0206	0.0263	0.0301	0.0190
21	0.0062	0.0065	0.0138	0.0136	0.0133	0.0194	0.0334	0.0151
22	0.0058	0.0059	0.0136	0.0134	0.0174	0.0201	0.0363	0.0169
23	0.0064	0.0060	0.0140	0.0143	0.0154	0.0265	0.0301	0.0169
24	0.0065	0.0062	0.0140	0.0137	0.0191	0.0230	0.0313	0.0172
25	0.0066	0.0066	0.0138	0.0139	0.0147	0.0184	0.0281	0.0170
Average	0.0060	......	0.0146	......	0.0175	0.0243	0.0332	0.0179

* Dogs fasted only one day. Not included in general averages.

by Jackson.[8, 9] By calculating the amount of calcium contained in the respective weight of connective tissue, blood, and tissue fluid, and subtracting this from the total, an accurate determination of the calcium in the pure muscle tissue may be obtained. The marked reduction of individual variation toward a constant level by the use of this method is evident from the figures in Table 2.

TABLE 2

Calcium Content of Smooth and Striated Muscle

Dog.	1 Stomach.	2 Stomach.	1 Retractor.	2 Retractor.	1 Sartorius.	2 Sartorius.
12	0.0143	0.0132	0.0244	0.0155	0.0335	0.0253
15	0.0175	0.0140	0.0265	0.0181	0.0291	0.0247
18	0.0165	0.0132	0.0250	0.0170	0.0342	0.0270
19	0.0154	0.0133	0.0187	0.0144	0.0284	0.0225
20	0.0206	0.0155	0.0263	0.0190	0.0301	0.0232
21	0.0133	0.0126	0.0194	0.0156	0.0334	0.0253
22	0.0174	0.0135	0.0201	0.0153	0.0363	0.0265
23	0.0154	0.0142	0.0265	0.0197	0.0301	0.0226
24	0.0191	0.0145	0.0230	0.0180	0.0313	0.0242
25	0.0147	0.0136	0.0184	0.0141	0.0281	0.0210
Average	0.0164	0.0138	0.0228	0.0167	0.0305	0.0242

1. Without correction for blood, lymph, and connective tissue.
2. After making quantitative histologic corrections.

Though the percentage of contaminating tissue in individual muscle tissues is extremely variable, the following general averages are:

Smooth muscle from stomach..............	84 per cent pure muscle
Smooth and striated from retractor........	72 per cent pure tissue
Striated muscle from sartorius.............	81 per cent pure tissue

CONCLUSIONS

1. By critical review of various methods used in physiologic quantitative analysis, a method has been adopted which seems most satisfactory for the determination of calcium in both blood and solid tissues.

2. A method for the rapid removal of tissues from the body makes it possible to use the term "fresh tissue" in a stricter sense.

3. A new morphologic method has been utilized in eliminating some of the important sources of error to quantitative chemical analysis of tissue, due to contamination of the pure tissue by the presence of other types of tissue.

4. The ratio of blood calcium to tissue calcium is probably a constant in normal dogs.

5. There appears to be a definite relation between the calcium content of the various types of muscle tissue in dog, cat, and rabbit, namely, cardiac < smooth < striated.

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THE PHARMACOLOGIC ACTION OF CERTAIN ETHERS AND ESTERS OF SALIGENIN*

HERMAN H. JENSEN

Benzyl alcohol saligenin and other aromatic alcohols have been shown to possess local anesthetic and antispasmodic action (Macht, Hirschfelder, Hjort). Hirschfelder and Quigley have also demonstrated that the local anesthetic action of benzyl alcohol and its derivatives is diminished when one of the inactive hydrogens (that is, in the ethylene of the ethyl alcohol carbinol group) is substituted by another radical; or, in other words, that the secondary aromatic alcohols are not as good local anesthetics as the primary, and that substitutions for both the ethyl hydrogens (tertiary alcohols) causes complete loss of local anesthetic action.

Although Hirschfelder, Lundholm, and Norrgard had demonstrated that methyl and ethyl substitutions on the phenolic hydroxyl of saligenin rendered the substances more irritating than saligenin, a more extensive study of this type of substitution products was desirable, particularly on account of the fact that they furnished some alcohols homologous with acetyl-salicylic acid.

The substances used in this research were prepared by Merrill C. Hart as by-products of an investigation of the phenolic alcohols and their derivatives as antiseptics and for the chemotherapy of the venereal diseases, with the aid of funds furnished by the United States Interdepartmental Social Hygiene Board. Their preparation has been described elsewhere (Hart, M. C. and Hirschfelder, A. D.: Some derivatives of saligenin, Jour. Am. Chem. Soc., 1921, xliii, 1688–1693).

The substances studied may be divided into three groups:

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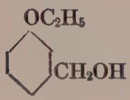
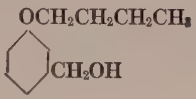
* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science, 1921. Abstract reprinted from the Proceedings of the Society for Experimental Biology and Medicine, 1921, xix, pp. 145–148. From the Department of Pharmacology, University of Minnesota, Minneapolis.

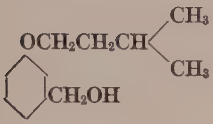
I. Ethers of saligenin with substitution on the phenolic hydroxyl, that is, the ethyl, *n*-butyl, iso-amyl, and benzyl ethers.



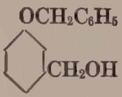
I.
Ethyl saligenin.



II.
N-Butyl saligenin.

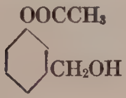


III.
Iso-amyl saligenin.

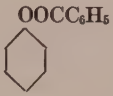


IV.
Benzyl saligenin.

II. Esters of saligenin with substitution on the phenolic hydroxyl (acetyl and monobenzoyl saligenin).

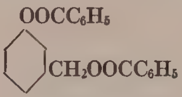


V.
Acetyl saligenin.



VI.
Benzoyl saligenin.

III. An ester with substitution on both hydroxyls (dibenzoyl saligenin).



VI.
Dibenzoyl saligenin.

All of these esters and ethers except the dibenzoyl compound are oily liquids, and the latter is a solid; and all are practically insoluble in water, but soluble in the usual organic solvents and in olive oil. Their pharmacologic properties were therefore studied by dissolving the substances in olive oil and emulsifying this with acacia by the Continental method.

Toxicity tests, made by determining the dose which was lethal for frogs in twenty-four hours, gave the following results: For the ethers, ethyl saligenin 0.5 mg. for each gram frog, *n*-butyl 0.25 mg., iso-amyl 0.12, benzyl 0.36 to 4 mg.; for the esters, acetyl saligenin 0.9 mg., benzoyl 1.0 mg., dibenzoyl 2.0 to 3.0 mg. All of these compounds are therefore more toxic than saligenin itself.

The local anesthetic action was tested by dipping the frog's foot into the emulsion and then into 1 per cent sulphuric acid. Two per cent emulsions were used. Anesthetic action set in from two to five minutes after exposure to the drug and lasted from ten to twenty-five minutes, except in the case of the normal butyl ether which was more prolonged and lasted from one to two hours, thus being more prolonged than that of saligenin. With the dibenzoyl ester no anesthesia whatever was obtained, even after thirty minutes' exposure to a 5 per cent emulsion. This corresponds to the results which have been obtained with benzyl benzoate and other benzyl esters by Macht and others.

All these substances are, however, very irritating. On the tongues of human beings they give rise to a bitter taste and an intense burning sensation which is most marked with the normal butyl, and least marked with the dibenzoyl ester.

On the contractions of excised segments of rabbits' duodenum in 400 mils of aërated Ringer-Langendorff solution at 38 to 39 degrees the addition of 2.5 mils of ethyl saligenin decreased the amplitude, slowed the rate, and finally caused complete inhibition; 1.5 mils of *n*-butyl, 0.5 mil of iso-amyl, 1.0 mil of benzoyl ester, and 10.0 mils of the dibenzoyl ester produced the same effects, but only 0.8 mil of the benzyl ether was required to produce complete inhibition, accompanied by a very marked lowering of tone. This lowering of tone was also striking with the iso-amyl, but not with the other ethers. In the case of the acetyl ester there was at first an increased amplitude (probably due to acetic acid from hydrolysis) with slowing of the rate, gradually followed by inhibition.

When ethyl and the iso-amyl ethers were injected intravenously into starved rabbits, anesthetized with ether, no visible effect on the contractions of the exposed small intestine could be observed through a glass window in the abdominal wall, but the *n*-butyl, the benzyl, the benzoyl and the dibenzoyl compounds all caused a definite inhibition of peristalsis and a well-marked dilatation of the intestine. Contrary to the findings of Mason and Piek, and in accord with the experiments of Macht, this inhibition after the injection of benzyl benzoate was also observed. When applied locally to the rabbit's intestine, all the compounds, with one exception, caused inhibition and dilatation. The acetic ester, however, on intravenous injection, augmented the peristalsis, and when applied locally produced spastic contractions.

All the emulsions, on intravenous injection, caused a fall of blood pressure, which varied from a sudden transitory fall in the case of the ethyl, *n*-butyl, and iso-amyl ethers to a more gradual and more prolonged fall after the acetyl, benzoyl, and dibenzoyl esters. The benzyl ether caused a sudden and more prolonged fall, which lasted four to five minutes. Control emulsions, injected at the same slow rate, produced no effect. Perfusion of the frog's circulatory system gave a marked vasoconstrictor effect, in striking contrast to the vasodilation obtained with emulsions of saligenin and benzyl benzoate. This constriction is probably due to irritation of the arterial walls.

CONCENTRATION OF UREA IN SALIVA*

PHILIP S. HENCH AND MARTHA ALDRICH

The quantitative excretion of urea in the urine and its concentration in blood have been studied extensively. That urea is excreted in the saliva, gastric juice, sweat, and feces has been recognized by various observers, but their work has been mainly qualitative. The present study, a preliminary report of the quantitative urea estimations of the saliva of a group of nephritic patients at the Clinic in the last three months, was made to determine whether the concentration of urea in saliva is of clinical importance in the diagnosis and prognosis of nephritis. Pettenkoffer and Wright, in 1848, first noted that urea was present in appreciable amounts in saliva. Later many isolated quantitative determinations were made, but the inexact methods then in use revealed data some of which were unreasonable in the light of modern technic.

A certain amount of nitrogen was constantly found in the saliva; this is probably mainly or wholly urea derived from the blood flowing to the gland, and constantly present because of its great physical property of diffusion in the body.

Anrep in his metabolic experiments on the salivary glands of dogs found that the nonmucin nitrogen in the nonselective excretion of the saliva remained at a constant level after a prolonged electrical stimulation of the chorda tympani, while mucin nitrogen from the selective secretion of the glands soon became exhausted. He believed the nonmucin nitrogen to be derived from the lymph and to be entirely independent of the selective secretion of the gland. This unanalyzed nonmucin nitrogen fraction of Anrep was possibly, in reality, urea, constantly present in the saliva as determined in these experiments.

In the estimation of the urea value of the saliva it is necessary to use the combined urea and ammonia nitrogen as the index of comparison on account of the proclivity of urea to hydrolyze rapidly into

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* Abstract of paper published in the Journal of the American Medical Association, 1922, lxxix, 1409–1412. From the Division of Medicine, Mayo Foundation.

ammonia. If the ammonia nitrogen present in the saliva were disregarded the urea values would be incorrectly lowered. Marked variations in the estimated urea value of saliva would, therefore, be obtained from hour to hour, depending on the amount of this hydrolysis. The combined urea and ammonia nitrogen value, however, is practically constant for each individual. It is not affected by prolonged salivation over a period of one hour, being constant throughout, nor are dilution factors introduced by the administration of pilocarpin.

In sixty-two of sixty-four estimations the combined urea and ammonia nitrogen in the saliva of normal persons fell between 6 and 13 mg. for each 100 c.c. Estimation in a group of forty nephritic patients with urea retention gave in every instance a higher combined urea and ammonia nitrogen value than 13 mg. for each 100 c.c.

A comparison between the blood and the saliva in a group of normal persons and those with urea retention showed that in each instance in which the blood urea nitrogen was 16 mg. or less for each 100 c.c. the salivary combined urea and ammonia nitrogen was 13 mg. or less for each 100 c.c., the values closely approximating each other. When, however, urea retention was evidenced by a rise in blood urea nitrogen the salivary values also rose in a curve closely approximating that of the blood urea nitrogen.

As an index of renal insufficiency the estimation of these salivary values is important. If blood examination is not practical or is impossible the saliva may be collected and examined, and will indicate the presence or absence of urea retention.

IX

GENERAL BACTERIOLOGY

THE SPECIFICITY OF BACTERIAL PROTEOLYTIC ENZYMES AND THEIR FORMATION*

HAROLD S. DIEHL

The property of specificity, which is usually ascribed to enzymes, is discussed and the improbability that there should be a specific enzyme for each protein is pointed out. A review of the literature shows a great diversity of results and conclusions, but gives the general impression that enzymes, at least proteolytic enzymes, are not specific. Experiments are described which were carried out in an attempt to procure further data on this point. Proteolytic enzymes alone were studied because as yet it is impossible to separate other enzymes from the bacterial cells in which they are formed. Several bacteria were cultivated on mediums of various content; then, by means of a Berkefeld filter, several cubic centimeters of sterile filtrate were obtained from the mediums. Of these sterile filtrates 0.5 c.c. was added to sterile gelatin and sterile casein solution. The gelatin was prepared according to the usual method. The casein solution was prepared according to the method described by Fuld and Gross. After the addition of the filtrates the tubes of gelatin and of casein, with the necessary controls, were incubated. At various intervals observations for evidences of gelatinolytic and caseinolytic enzyme action were made. On gelatin the enzymes caused liquefaction, while their caseinolytic activity was evidenced either by complete absence of a precipitate or a definitely smaller amount of precipitate than appeared in the controls, on the addition of acetic acid.

The organisms utilized for the experiments were, first, *Bacillus pyocyaneus;* second, *Bacillus prodigiosus;* and third, *Bacillus subtilis.* These three were chosen because of their strong proteolytic properties.

These three organisms were cultivated on eight different mediums: nutrient broth, gelatin, agar slants, a medium in which the only nitrogen was in the form of ammonium dibasic phosphate, this "inorganic medium" plus 1 per cent of peptone, plus 1 per cent of asparagin, plus 1 per cent of glycocoll, and plus 1 per cent of tyrosin.

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* Abstract of thesis submitted to the Graduate Faculty of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Arts, 1921. Published in full in the Journal of Infectious Diseases, 1919, xxiv, 347–361. From the Department of Bacteriology and Immunology, University of Minnesota, Minneapolis.

The results obtained in the experiments were: the sterile filtrates from agar, gelatin and broth digested both gelatin and casein; filtrates from the inorganic medium digested neither gelatin nor casein. When 1 per cent of peptone or 1 per cent of asparagin was added, the filtrates again digested both gelatin and casein; when 1 per cent of glycocoll was added, the filtrates digested gelatin but not casein, and when 1 per cent of tyrosin was added, the filtrates digested casein but not gelatin (Tabulation).

RESULTS OF EXPERIMENTS WITH VARIOUS MEDIUMS TO DETERMINE ENZYME PRODUCTION

Source of enzymes.	Liquefaction of gelatin.	Digestion of casein.
Gelatin:		
Bacillus pyocyaneus	+	+
Bacillus prodigiosus	+	+
Bacillus subtilis	+	+
Broth:		
Bacillus pyocyaneus	+	+
Bacillus prodigiosus	+	+
Bacillus subtilis	+	+
Agar slant:		
Bacillus pyocyaneus	+	+
Bacillus prodigiosus	+	+
Bacillus subtilis	+	+
"Inorganic mediums":		
Bacillus pyocyaneus	0	0
Bacillus prodigiosus	0	0
Bacillus subtilis	0	0
1 per cent peptone:		
Bacillus pyocyaneus	+	+
Bacillus prodigiosus	+	+
Bacillus subtilis	+	+
1 per cent asparagin:		
Bacillus pyocyaneus	+	+
Bacillus prodigiosus	+	+
Bacillus subtilis	+	+
1 per cent glycocoll:		
Bacillus pyocyaneus	+	0
Bacillus prodigiosus	+	0
Bacillus subtilis	+	0
1 per cent tyrosin:		
Bacillus pyocyaneus	0	+
Bacillus prodigiosus	0	+
Bacillus subtilis	0	+

The fact that nonspecific proteolytic enzymes can be obtained by cultivating certain bacteria on gelatin, casein, and nutrient broth is often mentioned in the literature and is of no special significance in this paper, except to show the basis for most of the conclusions with regard to the identity of proteolytic enzymes. The finding of no gelatinases or caseases on mediums without organic nitrogen is significant in the study of enzyme formation. It also seems to indicate that bacterial enzymes are not preformed in the bacterial cell, but are manufactured by the organism as the need for them arises. The formation of both gelatinases and caseases on mediums containing 1 per cent of peptone has very little significance because peptone is a substance of rather indefinite chemical composition, which is found as an intermediate step in the breaking down of all proteins. Hence, if peptone stimulated the production of any proteases, one would expect these to attack one protein as well as another. With asparagin as a source of nitrogen we have simple amin, but one which is contained in both gelatin and casein, as well as in most other proteins. Hence, if in mediums containing asparagin any proteolytic enzymes were formed it might be expected, as experiments show, that they would attack both gelatin and casein. Glycocoll is an amino acid which is present in gelatin, but not in casein. Experiments show that the enzymes which are formed on the mediums with glycocoll as a source of nitrogen will digest gelatin, but not casein. Tyrosin, on the other hand, is an amino acid which is contained in casein, but is absent from gelatin. The enzymes formed on mediums with tyrosin as a source of nitrogen digest casein, but do not attack gelatin.

From these results it appears that on mediums containing no organic nitrogen, no proteolytic enzymes were formed, and that on mediums containing but one amino acid as a source of nitrogen, the enzymes which are formed will attack only proteins which contain that particular amino acid. In other words, this enzyme seems specific for proteins containing the one amino acid. Thus, the enzymes formed on most amino acids tend to show very little specificity because most amino acids, like aspartic acid, are present in practically all of the proteins. Also, the ferments, which are formed on mediums containing either many amino acids or a few more complex nitrogenous compounds, would have the ability to attack large numbers of proteins, thus appearing to be entirely without specificity.

In reviewing certain of the properties of bacterial enzymes in the light of these experiments it seems, first, that the enzymes are dependent on some inherent properties of the organisms themselves; if this were not true, we would expect all bacteria to liberate the same enzymes; second, that a group of factors, including the temperature, the reaction of the medium, the time of growth, and so forth, which influence enzyme formation may be called general conditions; third, that the enzymes liberated are dependent, to a certain extent at least, on the composition of the medium in which they are formed.

This influence which the composition of the medium exerts on enzyme formation may account for some of the so-called irregularities of bacterial action which at times every bacteriologist meets.

The faculty of some bacteria to liberate certain enzymes and the specificity of these enzymes for certain amino acids will doubtless explain such apparent inconsistencies of bacterial action as the formation of indol by certain nonproteolytic bacteria, such as *Bacillus coli* and some of the dysentery group.

CONCLUSIONS

1. On a medium containing no organic nitrogen, no proteolytic enzymes are formed by bacteria.
2. On gelatin, casein, broth, agar, and peptone enzymes are formed which will digest both gelatin and casein.
3. The ferments obtained from mediums containing amino acids as the only source of organic nitrogen show various actions. The ones from asparagin digest both gelatin and casein; on glycocoll, no caseases are liberated, and on tyrosin, no gelatinases.
4. Proteolytic enzymes are apparently formed to correspond to the different amino acids present in the medium and will then attack these acids whether combined or free.
5. These enzymes are not preformed in the bacterial cell, but are dependent on the content of the medium on which they grow.
6. The specificity of proteolytic enzymes is resident in the amino acids composing the proteins and not in the proteins themselves.
7. Differences in the chemical constituents of mediums may account for many of the unverified "new strains" of bacteria, the differentiation of which is based on some minor phase of their action on culture mediums.

THE ELECTRICAL PROPERTIES OF BACTERIA*

HOFF DANIEL GOOD

A study was made of the movement of bacteria in a potential gradient by the use of specially constructed apparatus designed to eliminate errors commonly occurring in this kind of experimental work. The apparatus consisted of two upright electrode chambers connected by two systems of horizontal tubes, one of which was of large bore, the other carried a fine capillary tube in which movement of bacteria was observed by means of a microscope. The large bore tube served to keep the liquid level constant in the electrode chambers. Organisms studied included staphylococci, *Bacillus subtilis*, *Bacillus megaterium*, *Bacillus bienstocki*. Vegetative forms of bacteria were found to move toward the anode. This was a constant finding in both young and old cultures, and was the same with dead cells as with live cells. Movement toward the anode was constant with variations in the reaction of the suspending liquid. Bacterial spores were found always to move toward the cathode. In a suspension of both vegetative and spore forms migration of the vegetative cells and spore forms was observed to take place in opposite directions.

* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Arts, 1922. From the Department of Bacteriology and Immunology, University of Minnesota, Minneapolis.

THE OXYGEN CONTENT OF MEDIUMS IN RELATION TO SURFACE TENSION AND BACTERIAL GROWTH*

BERYL SPARKS GREEN

Since Larson has shown that the growth of bacteria is markedly altered in a medium of lowered surface tension, a study of the solubility of oxygen in relation to the surface tension of the solvent has been carried out in order to determine whether the observed changes in bacterial growth could be explained on this basis.

The solubility of oxygen was determined by the use of a Van Slyke blood gas apparatus. The solvents investigated included water, alcohol, acetone ether, glacial acetic acid, olive oil, Douglas salad oil, saturated salt solutions, broth, and peptone. Castor oil soap was added to salt solutions, to nutrient broth and to water, and the absorptive ability of such mixtures was compared with that of the original. The lowest tension obtained by the addition of soap was 32 dynes. Results were obtained as shown on page 579.

From the data it is noted that in general pure liquids of low surface tension absorb more oxygen than do those of high surface tension, but when the surface tension of a liquid is lowered by the addition of soap its absorptive ability is not increased. From this it appears that surface tension, in itself, does not influence the absorption of a gas by a liquid.

The efficacy of oil to keep a bacterial medium free from oxygen for anaërobic culture was demonstrated by layering oil to various depths over bacterial mediums containing alkaline pyrogallol. The rate of the penetration of oxygen through the oil into the medium could be measured by the increasing depth of the oxidation product. It was found that a layer of oil greatly retarded the entrance of oxygen. Tables were made showing the time rate of penetration of oxygen through oil layers of

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Arts, 1921. From the Department of Bacteriology, University of Minnesota, Minneapolis.

Fluids.	Surface tension.	Carbon dioxid absorbed.
Ether	16.5	2.70
Alcohol	22.0	1.40
Acetone	23.4	1.76
Glacial acetic acid	28.0	1.28
Salad oil	32.5	0.98
Olive oil	34.0	0.91
Water	72.5	0.34
Saturated salt solution	78.8	0.24
Saturated potassium carbonate	85.5	0.20
Saturated salt solution and soap and glycerin	54.5	0.24
Saturated potassium carbonate and soap	32.0	0.20
Broth	55.0	0.34
Peptone	54.5	0.34
1 per cent dextrive	52.0	0.34
Broth and soap	40.2	0.34
Water and soap	32.0	0.34

various thicknesses. The comparison of the foregoing results with the solubility of oxygen in oils would indicate that the rate of diffusion of oxygen through a layer of oil is not dependent on the solubility of oxygen in the oil. It was found that heat-coagulated tissue absorbs some oxygen and therefore aids in producing an anaërobic condition.

THE EFFECT OF THE SURFACE TENSION OF THE CULTURE MEDIUM ON THE GROWTH OF TUBERCULOSIS BACILLUS*

PU YUNG CHANG

It is well known that the tuberculosis bacillus, when grown on glycerin broth, forms a heavy pellicle. Very little is known regarding the cause of pellicle formation. It has generally been supposed to be due to the oxygen requirements of the microörganism. Larson, Cantwell, and Hartzell have shown that pellicle forming organisms will grow throughout the medium where the surface tension has been depressed sufficiently.

The object of the investigation here reported was to determine the surface tension at which the tuberculosis bacillus would grow throughout the medium rather than on its surface. It was found that the culture medium having a surface tension of from 40 to 45 dynes would suppress the pellicle formation and permit the organism to grow throughout the medium as any other bacteria, such as *Bacillus coli*, or the other organisms not given to forming a pellicle.

The interesting observation was made that potassium soap added to a medium would suppress pellicle formation of the bacillus several dynes higher than would a sodium soap. This indicates that the potassium soap exerts a specific wetting action on the germs, which is not true, to the same extent at least, of the sodium soap.

In studying the effect of the surface tension of the culture medium on the pathogenicity of the bacillus it was noted that a virulent culture, when grown on a medium of surface tension sufficiently low to suppress pellicle formation, lost its pathogenicity for guinea pigs. Guinea pigs inoculated with massive doses of such a culture failed to develop tuberculosis.

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota, in partial fulfilment of the requirements for the degree of Master of Arts, 1922. From the Department of Bacteriology and Immunology, University of Minnesota, Minneapolis.

Calmette reports similar results in growing the tuberculosis bacillus on bile medium. He offers no explanation of this phenomenon. I regard it as a phenomenon of wetting. When bacteria grow on the surface of a culture medium in the form of a pellicle they do this because of the inability of the culture medium to wet the organism, as has been shown by Larson and his associates. If this thought is carried into the discussion of the changed pathogenicity, it seems reasonable to assume that the factor of wetting would affect very markedly this property of an organism. When the tuberculosis bacillus, which is rich in wax and fat, is grown on the glycerin broth, the water and glycerin are apparently unable to wet the germ. When, however, soap is added, the surface tension is depressed. The presence of the soap facilitates the wetting and the organism is completely wetted by the surrounding medium. When such an organism is injected into a guinea pig the antibodies normally present in the blood serum immediately and thoroughly wet the organism and penetrate it, thereby destroying it. This, I believe, explains why pathogenetic organisms lose their pathogenicity when they become thoroughly wetted.

IMMUNOLOGIC STUDIES OF ACTINOMYCETES, WITH SPECIAL REFERENCE TO THE ACID-FAST SPECIES*

EDMOND N. NELSON

The serums of six of eight actinomycotic cattle fixed complement with four different antigens prepared from Actinomycetes isolated aërobically from lesions in cattle, and not with antigens prepared from saprophytic strains. The complement fixation test may be of diagnostic value in this disease.

The serum of a rabbit immunized against *Actinomyces bovis* fixed complement with antigens prepared from *Actinomyces bovis* and *Actinomyces maduræ*, but not with antigens prepared from the acid-fast varieties *Actinomyces asteroides* and *Actinomyces gypsoides*, or from *Mycobacterium tuberculosis.* The serums of rabbits immunized against *Actinomyces gypsoides* fixed complement equally with antigens prepared from *Actinomyces gypsoides* and *Actinomyces asteroides*, and in lower dilutions with *Mycobacterium tuberculosis*, but not at all with *Actinomyces bovis* and *Actinomyces maduræ.* The serums of rabbits immunized against *Mycobacterium tuberculosis* fixed complement with the homologous antigen, and in lower dilutions with antigens prepared from the acid-fast Actinomycetes, *Actinomyces asteroides* and *Actinomyces gypsoides*, but not with *Actinomyces bovis* and *Actinomyces maduræ.* It would seem, therefore, that the acid-fast Actinomycetes are more closely related to the acid-fast bacteria than to the non acid-fast Actinomycetes.

Actinomyces gypsoides does not secrete a soluble toxin, but forms a very potent endotoxin. By careful vaccination there can be produced in rabbits an active protective immunity. The serum of such rabbits injected into guinea pigs gives the latter partial protection.

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A STUDY OF THE RELATION BETWEEN THE FIXED AND FREE SALTS OF BACTERIA*

MADELEINE GUILLEMIN

When bacterial cells, suspended in distilled water, are killed by heat and allowed to stand for about two hours, there is a rapid exosmosis of salts from the cells. The salts which pass out on the death of the cell are the free salts, while those tied up in some way in the protoplasms and remaining in the cell after diffusion and centrifugalization are the fixed salts. The nature and amount of the free and fixed salts were determined by analysis.

The amount of free or unbound salts in bacteria exceeds the amount of fixed salts.

The bacteria, a strain of *Bacillus coli*, were grown on meat extract peptone broth containing 0.5 per cent of sodium chlorid. The organisms were then centrifuged out, washed, suspended in distilled water, killed by heating to 60 C. for thirty minutes, and allowed to stand for two hours. The cells were again separated from the liquid by centrifuging. The diffusate was evaporated until dry and analyzed, while the organisms were dried and ashed, and the ash was analyzed.

The results showed that salts passed out of bacterial cells when killed by heat and suspended in distilled water; moreover, the greater part of the salt content of the cells diffused out, for the weight of the free salts was greater than the weight of the fixed salts. Calcium, magnesium, sodium, potassium, and phosphates were the elements found most abundantly. Sodium and potassium showed interesting results, the former occurring mainly in the diffusate, the latter largely in the fixed salts.

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* Abstract of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Arts, 1921. From the Department of Bacteriology and Immunology, University of Minnesota, Minneapolis.

STUDIES IN POSTMORTEM BACTERIOLOGY: VALUE AND IMPORTANCE OF CULTURES MADE POSTMORTEM*

ALFRED S. GIORDANO AND ARLIE R. BARNES

Since certain deaths occurring in the Mayo Clinic could not be explained on the basis of anatomic changes found at necropsy, postmortem bacteriologic studies were undertaken by the authors, and they are now considered to be due to chemical changes in the cells. Infections undoubtedly play an important rôle in initiating these chemical changes. Bacteriologic cultures were made at necropsy of 213 cases. In 206 cases in which the blood was cultured, it was positive in eighty, 38.8 per cent; in 190 cases in which the spleen was cultured it was positive in seventy-five, 39.4 per cent. The spleen serves as well as, if not better than, the heart's blood for determining a terminal bacteremia.

Scrupulous attention to details of technic is necessary at all stages of bacteriologic examinations at necropsy. The organ to be cultured is seared with a red hot spatula and a sterile pipette thrust through the seared surface and the desired amount of material aspirated. Cultures are made in glucose broth prepared according to the method of Rosenow, because, as Rosenow has pointed out, "the bottom of the tube is rendered anaërobic while the top necessarily remains aërobic and the space between represents a gradient of oxygen pressure intermediate between the two extremes."

The reliability of postmortem cultures was tested in twenty-two cases, in fifteen of which the results of antemortem cultures of examinations were in harmony with the postmortem cultures. The differences in the results, moreover, may be explained by evidence of a superimposed process revealed at necropsy. Uniformly negative results in cases ordinarily regarded as noninfectious in type strengthens the belief in the reliability of postmortem cultures. Failure to obtain positive blood cultures in fifty-one cases in which an abundant focus of infection was demonstrated at necropsy leads to the belief that invasion of the blood stream after death must occur only rarely, at least not within twenty-three hours.

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* Abstract of paper published in full in the Journal of Laboratory and Clinical Medicine, 1922, vii, 538–546. From the Section on Pathologic Anatomy, Mayo Clinic.

The fact that terminal invasion may occur is not denied; it may, in fact, be the most important contributory factor in the cause of death, as evidenced by the case of a patient with general lymphosarcomatosis of the abdomen. Necropsy revealed in addition to this a general fibrinous peritonitis and pleuritis from which, as well as from the blood stream, a pure culture of hemolytic streptococcus was isolated. Although the infection was terminal, it was certainly the immediate cause of death.

Postmortem bacteriology, which may modify or strengthen necropsy and clinical diagnosis, may also be the only means of revealing the true cause of death. For example, in a mysterious and apparently unrelated short series of deaths not readily explicable on clinical or pathologic grounds, careful routine bacteriologic studies showed that these deaths probably resulted from a tetanus contaminated catgut. In all probability the organism would not have been recovered if the media routinely employed had not been suitable for the growth of anaërobic bacteria.

A sustained, progressive increase in the number of positive results obtained at successive hours after death has not been observed in the series of cases studied.

BACTERIA RECOVERED POSTMORTEM WITH SPECIAL REFERENCE TO SELECTIVE LOCALIZATION AND FOCAL INFECTION*

ARLIE R. BARNES AND ALFRED S. GIORDANO

The making of routine cultures at postmortem in the Mayo Clinic afforded opportunity for studying the possible etiologic rôle of foci of infection in thirteen morbid processes comprising cases of nephritis, peptic ulcer, meningitis, and peritonitis.

Teeth incriminated by previous roentgen-ray studies were removed under strict aseptic conditions and the organisms in the infected area cultured in dextrose-brain-broth mediums. In cases of peptic ulcer and nephritis suspensions of the organisms cultured were injected intravenously into rabbits. In an investigation of meningitis rabbits were injected both intravenously and intracerebrally. Mice, guinea pigs, and rabbits were used in the study of localization of organisms in the peritoneum.

In general, localization of organisms was clearly demonstrated in nephritis, peptic ulcer, meningitis, and peritonitis. In one case in which both peptic ulcers and focal abscesses of the kidneys were present localizations in both these structures were encountered in experimental animals. Two organisms were present in this case; the streptococcus localized chiefly in the stomach, and staphylococcus exhibited a predominant selective affinity for the kidneys. In a case of primary peritonitis a culture from an infected tooth localized in the peritoneum of mice, guinea pigs, and rabbits. Control injections of morphologically similar organisms failed to exhibit this power of localization.

The study demonstrates that organisms recovered from foci a few hours after death possess a definite localizing power in certain cases. Necropsy affords an opportunity to study all possible foci, the lesions to which they may be related, and the exact pathology of those lesions.

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* Abstract of paper published in full in the Indiana State Medical Journal, 1922, xv, 1–5. From the Section on Pathologic Anatomy, Mayo Clinic.

X

GENERAL MISCELLANEOUS

A CONSIDERATION OF THE LAWS OF HEREDITY AND THEIR APPLICATION TO VARIOUS CONDITIONS IN MAN*

J. ARTHUR BUCHANAN

Heredity is a science devoted to the study of the phenomena of breeding.

The mechanism of heredity came into play with the appearance of bisexual life on the surface of the earth. Its laws will continue to function until such life becomes extinct. The efforts of ancient, of medieval, and of modern investigators to unravel the workings of the mechanism of heredity form an interesting chapter in the development of biologic knowledge.[12]

The physicobiologic characters, which are transmitted to subsequent generations by means of the germ plasm, furnish the concrete evidences for studies in heredity. A biologic character signifies a type of physical and chemical composition possessed by individuals, by which they may be differentiated. Characters are rendered physically immortal by heredity, and the study of heredity becomes, in consequence, an investigation of the mechanism of physical immortality. The vehicles on which the transmission of the characters depends are the nuclear structures, chromosomes in all germ cells, and in certain instances the cytoplasm of the germ cells. The hereditary substances in the chromosomes and cytoplastic substances together comprise the germ plasm. The germ cells or gametes in man are the ova and the spermatozoa.

Heredity never deals with the etiologic factors of disease. Any characters appearing in man that can be proved hereditary are normal, biologically speaking, regardless of how the characters may unfit their bearer for harmonious coöperation in the economic and social programs of civilization. This conception becomes clear when it is remembered that characters are brought to their bearer as an integral part of the stuff from which he developed, and that there is no alteration from the normal course of life. The factor on which the character depends is in the germ plasm. The character undergoes development along a fairly fixed line, as a component part of the body in which it appears. Hereditary characters in all plants and animals, and even in man in certain instances, are considered as expressions of normal features. The characters in man which embarrass his participation in all or certain parts of his duties and pleasures are looked on as expressions of disease. A man with an untoward hereditary character cannot be otherwise from a biologic and physiologic standpoint. The embarrassing characters are the physical expression of the type of stuff of which he is composed genetically, and not the expression of pathologic processes.

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* Thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine, 1922. From the Section on Medicine, Mayo Clinic. Reprinted from Amer. Jour. of Med. Sc., 1923. Copyright by Lea & Febiger, Philadelphia.

By heredity the quantitative and qualitative characters in all bisexual species are kept extant and limited. Under similar conditions of reproduction the numerical expression of the transmission of these characters follows very closely, or is reducible to, a fairly definite ratio. A character once proved hereditary is always hereditary, but not hereditary on a percentage basis.

The science of heredity includes the study of the intermediate as well as of the immediate stage of certain features of the life cycle. The ova and spermatozoa form the intermediate stage of the life cycle in man. The rearrangement[8] of chromosomes which occurs following their union furnishes the fundamental basis for the study of the method of production of the tangible evidences of heredity in the immediate stage, the corporal stage, of the life cycle.

It is remarkable that heredity, a science so familiar not only to physicians, but to all reading men, whose principles are so easily gathered from the works of biologists, should be characterized by a lack of accuracy in medical literature.

Heredity as ordinarily used by medical writers means the presence of a like condition in parent and child. This occurrence is usually described as one of the etiologic factors for the disease under consideration. The laws of heredity which have been established are at variance with this usage.

Kölreuter made the first systematic investigation of hybridization, which is the first stage resulting from the crossing of parents with different inheritable characters. By his experiments he established the fact that the hybrid offspring generally looks as like the male as the female parent.

Mendel carried the work of Kölreuter one step farther by mating hybrid with hybrid. When the products of this mating were examined, he found that the parental characters which entered into the formation of the hybrid were separated in a peculiarly striking manner, and that the hybrid reappeared in its identical form. To this phenomenon Mendel applied the phrase, "segregation of characters." This is now known as the first law of heredity. Mendel believed that in the offspring of a mating all characters are segregated independently, and that there is no interrelationship in the transmission of characters. This belief is usually spoken of as the "independent assortment of characters," and is the second law of Mendel and of the science of heredity. This law has been found to be only partially true.

Since the time of Mendel four other laws have been derived from experiments carried out on plants and animals. They are known as (1) linkage, and its corollary, crossing over, (2) linear order of genes, (3) interference, and (4) limitation of the linkage groups. They have been carefully studied by Morgan. Linkage of characters has been found to occur in man. The corollary and the other three laws have not yet been worked out in man.

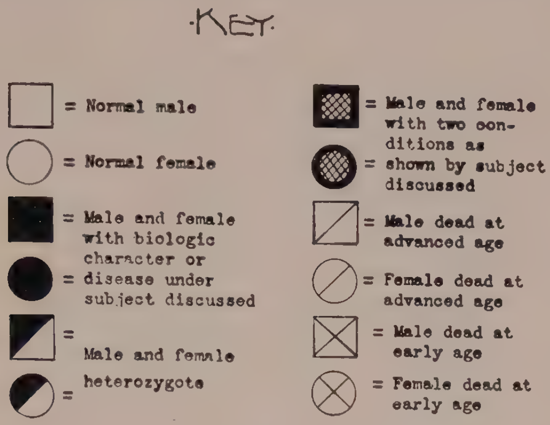
The discovery of the spermatozoön in man by Leeuwenhoek, the ovum in mammals by Von Baer, the cell by Schleiden and Schwann, the chromosomes by Van Beneden, the theory of cellular continuity by Virchow, the theory of germinal continuity by Nussbaum, furnished the material on which Weismann evolved the theory of the germ plasm. This theory clearly isolated the ultimate units on which physicobiologic characters must depend. The theoretic units are located in the germ plasm, and in their finest division are known as "biophors"; aggregations of biophors are known as "determiners," and the latter when grouped together are known as "ids." Groups of ids are called "idants," which are identical with chromosomes. Determiners are the fundamental aggregations of hereditary units in the germ plasm. Weismann vivified the significance of the spermatozoön and ovum with their nuclear and cytoplastic structures as the medium for the transmission of the ultimate units of hereditary characters.

The terminology used in studies in heredity is very simple. The parental generation, or the stock from which a series of studies has been made, is expressed by the symbol, *P*. The first product resulting from a mating of the parental generation in which unlike characters are crossed is known as the hybrid, and this stage is spoken of as the first filial generation. By mating members of the first filial generation the second filial generation is obtained. This generation was the important one in the studies of Mendel. All generations, except the parental, are designated by the letter *F*, and a subnumeral which indicates the generation under consideration. The term "homozygote" is used to designate individuals who are pure bred for a particular character. The homozygote, when crossed with a homozygote with like characters, always breeds true to the characters present. The term "heterozygote" refers to an individual who, while possessing a certain character in his somatic cells, because of certain properties in the germinal cells, has the ability of transmitting not only a character present in the somatic cells, but a character which is concealed or dormant in the germinal cells. The determiners for the dormant and evident characters are located in the germ plasm.

The discovery of the heterozygous property of plants was one of the most fundamental discoveries made by Mendel. In man the heterozygous person can be determined only by breeding, whereas in plants the knowledge of the nature of the parental generation furnishes information which enables an observer of plant breeding to determine in certain instances by physical inspection the homozygous and heterozygous types.

The property of the hybrid in plants to conceal one character while another was evident led Mendel to introduce the words "dominant" and "recessive." The character which is visibly represented in the hybrid is spoken of as dominant, while the other is spoken of as recessive. These words have been used in connection with the study of heredity in man, but erroneously so, as there is no direct way of determining which of the two characters will be dominant, because when two persons are mated to produce a cross of different characters, instead of a hybrid generation, there is an immediate progression to the segregation of the characters introduced in the cross with the production of both homozygous and heterozygous individuals, just as occurs in plants and fowls in the second filial generation. The first filial generation—hybrid stage in man—is absent. The terms "dormant" and "evident" are more expressive when speaking of hereditary characters in man.

Mendel left no graphic illustration of his work which was carried out on species and subspecies of the edible pea (Pisum sativium) and species of the hawkweed (Hieracium), but Correns, who discovered Mendel's work, confirmed and extended it and visualized the parental


KEY
= Normal male
= Normal female
= Male and female with biologic character or disease under subject discussed
= Male and female heterozygote
= Male and female with two conditions as shown by subject discussed
= Male dead at advanced age
= Female dead at advanced age
= Male dead at early age
= Female dead at early age

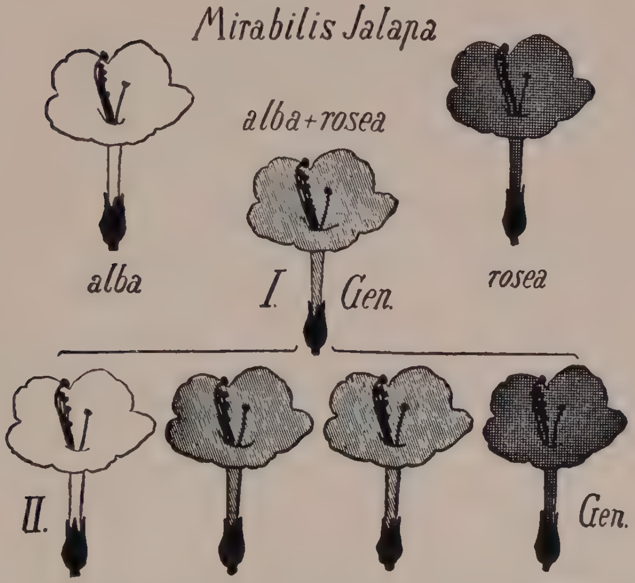


FIG. 206.—A diagram to show inheritance of flower color crosses of Mirabilis, the "four-o'clock." *Alba*, white parent; *rosea*, red parent; *alba-rosea*, the unfixable F_1 heterozygote of intermediate color, pink. First generation $= F_1$. Second generation $= F_2$. (After Correns.)

generation, the first filial generation, and the second filial generation during which the segregation of characters took place (Fig. 206). In this experiment the four o'clock was used. A red flower (character red) was crossed with a white flower (character white). The result was a pink hybrid. When two of the hybrids were mated together their offspring consisted of one red flower, one white, and two pink flowers commonly spoken of as heterozygote. The separating was the clearest possible example of what Mendel meant by the expression "segregation of characters." The red and white if crossed with red and white respectively breed only red and white respectively, whereas if the pink flowers of the second filial generation are crossed with pink flowers the segregation of characters repeats itself.

By a statistical investigation of many crosses Mendel established the now famous 3 to 1 ratio which is approximate and not absolute as shown by his investigations. He found in Experiment 1, a ratio of 2.96 to 1; in Experiment 2, 3.01 to 1; in Experiment 3, 3.15 to 1; in Experiment 4, 2.95 to 1; in Experiment 5, 2.82 to 1; in Experiment 6, 3.14 to 1; and in Experiment 7, 2.84 to 1. These figures show a rather narrow range of possibilities.

In the study of heredity in man the absence of the hybrid stage presents distinct obstacles to the direct application of the scheme used by Mendel in his investigations. The heterozygote in man is identical genetically with the hybrid of plants. Mendel demonstrated the segregation of characters by mating hybrids, which were the offspring of the same parents. The only similar biologic and genetic situation in man would be the crossing of sister and brother heterozygotes, provided their heterozygous nature could be proved beforehand. Such a cross in man is clearly impossible. Furthermore, it is quite impossible to say in advance of a mating, whether or not a cross is of heterozygotes, or of homozygotes and heterozygotes. The evident character is always discernible, but the dormant character in man exists without any evidence. It is also often impossible to determine after studying the offspring resulting from a cross between two persons whether the parental generation was heterozygous or homozygous. The homozygous nature of both parents is demonstrated when all the children possess the same characters as the parents.

These difficulties make it impossible to derive mendelian ratios directly by tabulating the products of crosses in man. Through a long period it may be possible to demonstrate which characters may appear in certain combinations only as evident or dormant characters. Hitherto no attempt has been made to prove this essential possibility in man, but by such an indirect procedure dominant and recessive characters can be determined. After the relationship of the dormant and evident characters in the heterozygote has been worked out, it will still be impossible to determine in advance of mating the homozygous or heterozygous nature of any particular person, unless his ancestors have been previously proved to be homozygous for the character under consideration. The accuracy of mendelian ratios in man will be lessened for a long time to come on account of these obstacles.

Certain requirements are necessary in order to determine if a character or condition in man is hereditary and to establish its relationship to another character. The character must be arbitrarily defined, and a contrasted character must be selected. When two characters are crossed, at least three, and preferably four or more children must result in order to observe the segregation of the characters and to establish their numerical relationships. A cross in man where only two characters are concerned needs investigation through but two generations. The evident characters will be discernible, but the recipients of the dormant characters cannot be distinguished. This fact must be borne in mind constantly, for heterozygous mates will reproduce their ancestors; unless this faculty is recalled, many conditions will be considered hereditary on a percentage basis or else not considered hereditary at all. The heterozygous principle has been responsible for immeasurable misunderstandings in the study of heredity in man. In cases in which three or four characters are under investigation the four grandparents, the parents, and a final generation of preferably four or more children must be studied; a final generation of less than three children furnishes data of no conclusive value. The *sine qua non* of an hereditary investigation is the knowledge of the characters represented in the germ plasm of the ancestors of the individuals under consideration.

THE INHERITANCE OF THE BLOOD GROUP: STUDY I

In 1900 Shattock observed that the serum of patients suffering from certain diseases agglutinated the red blood cells of healthy men. He also noted the persistence of the agglutinative phenomena during the convalescence from the diseases. In 1901 Landsteiner discovered that the red blood cells of healthy men, because of certain agglutinative properties of the serum, could be classified into three groups. A fourth blood group, Group 1 of the Moss classification, was discovered by Decastello and Sturli in 1902. In 1907 Jansky made independent observations and reported the existence of four blood groups. The observations were reported independently by Moss in the United States in 1909. The four blood groups known today are arbitrarily designated as Group 1, Group II, Group III, and Group IV. They have been classified by Jansky and by Moss. Their classifications differ in that Jansky's Group I is the Group IV of Moss and vice versa. The scheme of Moss has been concisely presented by Sandford (Fig. 207). I have followed the Moss classification, although the priority of Jansky is recognized as adopted by the American Association of immunologists, the Society of American Bacteriologists, and the Association of Pathologists and Bacteriologists.*

The mendelian transmission of blood group to subsequent generations by the germ cells has been suspected[37]; some definite evidence has been presented,[18, 39] but certain difficulties remain. This study was made in an attempt to obviate these difficulties.

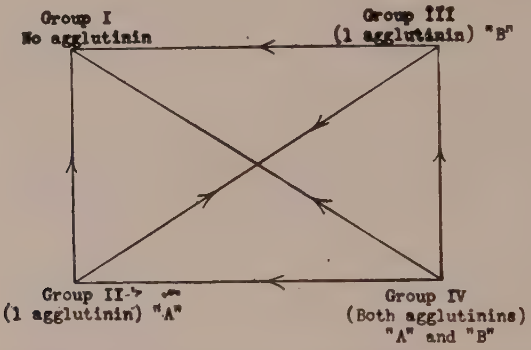


FIG. 207.—The corpuscles of the various groups are agglutinated by the serums of the groups from which the arrows lead. (After Sanford.)

The material studied was obtained in a unique manner. In discussing my desire to add further data concerning the inheritance of blood group with Dr. W. A. Evans, he suggested that a notice (Fig. 208) be inserted in his health column in the Chicago Tribune. It appeared on April 26, 1921. The same request subsequently appeared in all the publications of the Tribune Syndicate. Through the kindness of the Eugenics Record Office the interest of Mr. A. E. Wiggam was aroused, and a similar request appeared in the Physical Culture Magazine, August, 1921. The replies to these requests were mailed to me.

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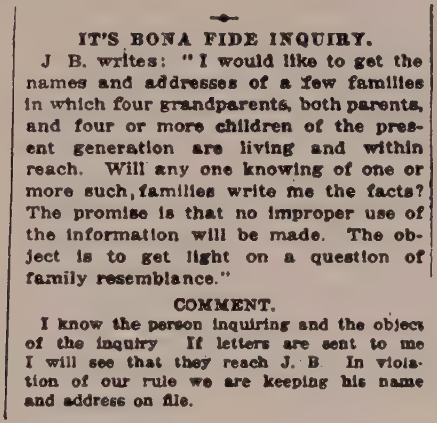
* Article on Isohemagglutination: Jour. Am. Med. Assn., 1921, lxxvi, 130.

Each member of the family was mailed a 3 c.c. glass tube which contained 1 to 2 c.c. of 2 per cent sodium citrate solution. The tubes were well corked, packed in cotton in an ordinary mailing tube, and sent by first class mail. At the same time instructions were forwarded for collecting blood from a needle stab in the finger, and for labelling and remailing the tubes. The instructions were accompanied by a letter requesting the coöperation of the family in the work. If the first letter failed, a follow-up letter was sent. One tube was broken; twice hemolysis of the red cells occurred, so that second specimens had to be obtained. The cells were grouped with known Groups II and III serums and checked with homologous serums. Families suitable for this study are very scarce. There is not such a family on record at the Eugenics Record Office, Cold Springs Harbor, New York.*



IT'S BONA FIDE INQUIRY.

J B. writes: "I would like to get the names and addresses of a few families in which four grandparents, both parents, and four or more children of the present generation are living and within reach. Will any one knowing of one or more such families write me the facts? The promise is that no improper use of the information will be made. The object is to get light on a question of family resemblance."

COMMENT.

I know the person inquiring and the object of the inquiry If letters are sent to me I will see that they reach J. B In violation of our rule we are keeping his name and address on file.

FIG. 208.—Insert from Chicago Tribune, April 26, 1921. (Kindness of Dr. W. A. Evans.)

In 1908 Ottenberg first suspected that the blood group was hereditary and transmitted to subsequent generations according to the laws of Mendel. In 1910 von Dungern and Hirschfeld reported seventy-two families (348 persons) in which the grouping of the blood had been carried through two generations. They concluded that blood group was hereditary and transmitted according to the mendelian rules. Ottenberg,[38] in 1921, established certain formulas which he considered to be representative of the blood groups. In this study, in contradistinction to Ottenberg's formulas, I have used the terms Group I, Group II, Group III, and Group IV as expressive of a specific biologic property of the blood of man. The factor for blood group is considered as comparable to those unexplained factors on which the unit characters height, shape, size, color, and so forth, in plants and animals depend. The exact formulas of the ultimate units on which hereditary characters depend are unknown.

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* I owe my thanks to Mr. E. C. Myers and Dr. J. I. Mershon, Mt. Carroll, Illinois; Dr. H. B. Cole and Dr. B. P. Flinn, Redwood Falls, Minnesota; Dr. R. A. Jacobson and Dr. C. F. Crow, Exira, Iowa; Dr. Greenleaf, Atlantic, Iowa, and Dr. C. C. Bassett, Goodand, Indiana, for their assistance in the work.

If it is assumed as a premise that blood group is expressive of an hereditary character dependent on a unit factor, comparable to that for color of flowers, height of plants, and so forth, it becomes necessary to present data to ascertain if blood group is transmitted between generations in a manner similar to that occurring in plants and flowers. The data presented in Figure 209 consist of the crossing of Group II with Group IV through three generations. If Figure 209 is compared with Figure 206 the absence of the hybrid stage or stage of the first filial generation in Figure 209 will be noted; otherwise a new blood group having, to a certain extent, the characteristics of both parents would result. In the third generation of the family studied one child in Group IV and three children in Group II appeared. The blood groups present in the previous generations appeared in the final generation. No other blood groups appeared. If the phenomena observed in the third generation of this family were considered as illustrative of the first law of Mendel, it might be assumed that two of the children were homozygous and two were heterozygous, as occurs in the mendelian segregation of characters. It was impossible to demonstrate a basis for the assumption in this family, as it would have been necessary to group the progeny of all four children in the family. The result would have

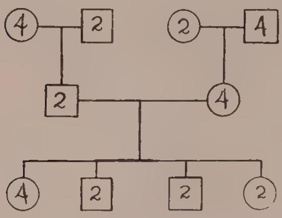

Fig. 209.—Transmission of blood Groups IV and II through three generations.

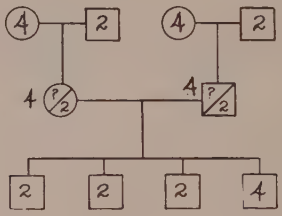

Fig. 210.—Transmission of Groups IV and II to the third generation because of the heterozygous nature of one of the parents in the second generation.

been influenced by groups introduced by marriage, and the data obtained might or might not have been of any conclusive value.

The evidence that there are heterozygous individuals for blood group produced by the crossing of Group II and Group IV is shown in Figure 210. The parental generation on both sides of the family consisted of the union of Group II with Group IV. Both families had a child in Group II. The mating of these children resulted in three children in Group II and one child in Group IV. If the blood group is hereditary, the factor for the Group IV must have been present in the germ plasm of either the male or the female parent, for there is no other mechanism in heredity by which it could have appeared in the final generation. A like situation is shown in Figure 211. The blood of a heterozygote is not different from the blood of a homozygote. The difference is in the germ plasm alone.

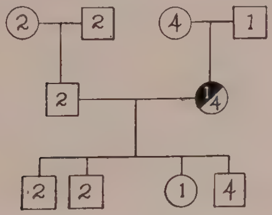

Fig. 211.—The segregation in the third generation of all the characters introduced by the ancestors. The female in the second generation was a heterozygote.

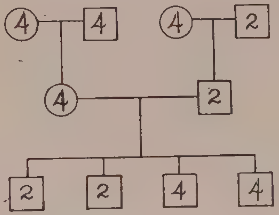

Fig. 212.—Transmission of blood Groups II and IV through three generations. There is no method of demonstrating the homozygous or heterozygous status of the male in the second generation.

The heterozygous property is again illustrated in Figure 212. In the parental generation on the left, the cross consisted of presumably homozygous Group II parents, and on the right a Group IV was crossed with a Group I. The result was a Group II on the left and a Group IV on the right. The final generation showed two children in Group II, one in Group I, and one in Group IV. This happened because of the heterozygous nature of the parental Group IV on the right. Figure 213 is also a very clear demonstration that blood group is a distinct hereditary character, as all the characters concerned in the primary generation reappeared in the final generation. The same phenomenon is observed in Figure 214 where Groups III and IV appear as the expression of the heterozygous principle.

The homozygous nature of blood group is illustrated in Figure 215. In this family the parental crossings on both sides resulted in children in Group II, which on being crossed produced four children in Group II. The same situation is shown in Figure 216 where Group IV is the homozygous character. Ottenberg, in 1908, demonstrated the homozygous nature of Group III. He reported a father, mother, and four children all in Group III. The effect of crossing Groups III and IV is shown in Figure 207. The homozygous nature of Group I has not yet been demonstrated, but it seems reasonable to suppose, from its be-

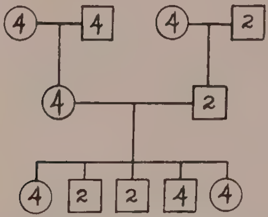

Fig. 213.—Transmission of Groups IV and II through three generations.

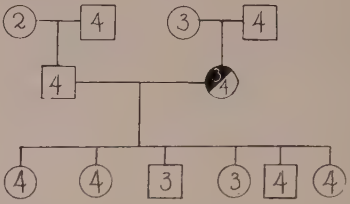

Fig. 214.—Transmission of blood Groups IV and III through three generations by means of a heterozygous female in the second generation.

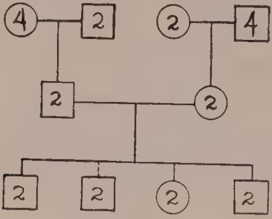

Fig. 215.—Segregation of pure Group II in the second generation as indicated by all the children of the third generation being in Group II.

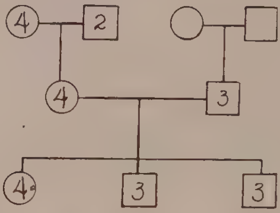

Fig. 216.—Result of crossing pure Groups IV and III through two generations.

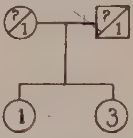

Fig. 217.—The value of the three generation study for determining the origin of blood group. The Group III is explainable only by information obtained through families as in Figure 211.

havior when crossed with other blood groups, that it could appear in the homozygous state as well as in the heterozygous state (Figs. 211, 217, and 218).

The expressions "dominant" and "recessive" are frequently heard in discussing the inheritance of any character. Mendel described this usage thus: "Those characters which are transmitted entire or almost unchanged in the hybridization and, therefore, in themselves constitute the characters of the hybrid, are termed the 'dominant,' and those which become latent in the process, 'recessive.' The expression 'recessive' has been chosen because the characters thereby designated withdraw or entirely disappear in the hybrid, but nevertheless reappear unchanged in their progeny." The hybrid state is absent in all families I have studied, as well as in all the families grouped by von Dungern and Hirschfeld, and by Ottenberg.[39] The absence of the hybrid stage in man is shown in the study of all families reported as illustrative of the transmission of hereditary characters of all kinds, unless the sex linkage phenomenon, as seen in hemophilia and in color blindness may be interpreted as expressive of the hybrid stage. It is, then, improper to use the term dominant and recessive in connection with heredity in man until further studies are made. As the heterozygotes in plants are identical physically and genetically with the plant hybrid, and as the heterozygote in man behaves in the same manner as the heterozygote in plants, it may be possible to work in a reverse manner in order to determine which blood groups in various combinations can appear only as the dormant and evident combinations. If there is no reversal in the relationship of the dormant and evident characters, dominance of one character to another may be spoken of in its true sense. If there is reversal, the use of the expressions dominant and recessive will remain meaningless. The settlement of this point is, however, not of vital importance in the study of heredity in man; it is more a matter of accuracy and correct usage. It could be of importance, however, in the use of the blood group in the adjudication of medicolegal disputes. Until it is proved which character may appear as dormant in certain unions the use of blood group in medicolegal affairs will be fraught with great danger unless the blood grouping is carried in a definite scheme into the preceding generations, and even then the result may be inconclusive (Fig. 223). The possibilities of the medicolegal value of the blood group were mentioned by von Dungern and Hirschfeld in 1910 and by Giraud in 1919.

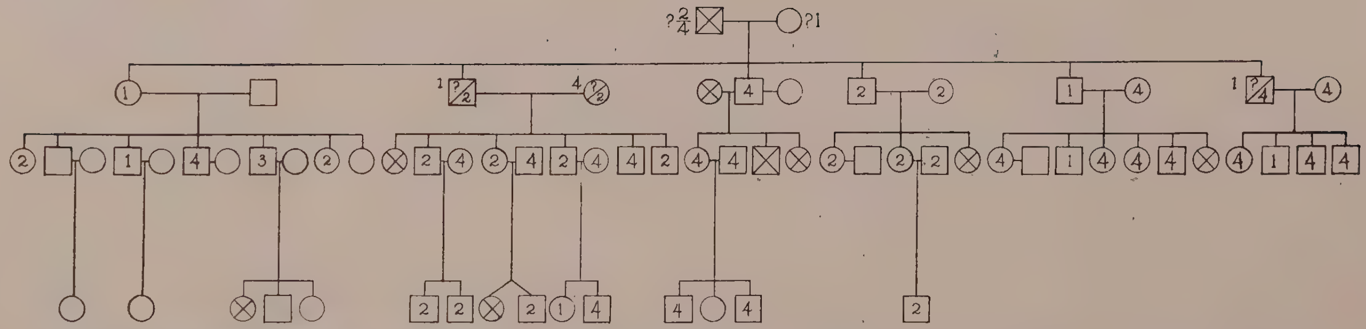

FIG. 218.—The parental generation in this family (Tink) can be presumed to be a heterozygous male (Groups II and IV) crossed by a homozygous female (Group I). The segregation of these characters in the first generation is striking. Additional undetermined groups are introduced into the second generation by marriage. If the heterozygous status of man for the blood group were not demonstrable, the appearance of the Group IV in the third generation of the second family, and the Group I in the third generation of the sixth family and in the fourth generation in the third family would be inexplicable by the science of heredity. The difficulties in the medicolegal application of the blood group are sharply shown in this family, and the inability to prove by the study of isolated small families the transmission of the blood group by the germ plasm. (Information obtained through the courtesy of Mr. F. T. Jung, Sheboygan, Wisconsin.)

Ottenberg[38] has presented data in an endeavor to demonstrate the possible blood groups that may result from crossing two persons in the same or different groups. His conclusions were made in conformity with formulas which he had outlined as representative of the various blood groups.

The acceptance by Ottenberg of the hypothesis that in the inheritance of the blood group agglutinogens *A* and *B* of the red cells behaved as dominant characters, while the agglutinins *a* and *b* of the serum behaved as recessive characters is stimulated by the belief that Group IV (Group I of Jansky) can exist only in a pure state (recessive). Ottenberg also believes in the existence in man of a hybrid for blood group, in a variable relationship in the groups of the supposed dominant and recessive characters, and in the union of *A* and *B* to produce Group IV (*A*, *B*). These beliefs are entirely groundless in the light of Mendel's experiments. The dominant and recessive characters are determined by means of the hybrid. A hybrid stage for the blood group is absent in man. Even if Group IV (Group I of Jansky) were a recessive character to one blood group evidence would have to be presented to establish its relationship to the remaining two groups. My study clearly shows that unions of Group IV (Group I of Jansky) may result in offspring in the other three groups, depending solely on the groups present in previous generations. By crossing a Group II with a Group III it is shown that Group IV (*A*, *B*) is not the result of the union of *A* and *B*. If a hybrid stage in man existed this result would be possible, and all the children would be in Group IV (*A*, *B*). The serum of this hybrid would agglutinate the cells of Groups II and III, and the cells would be agglutinated by the serum of Groups II and III. Such a combination does not exist. Furthermore, if Group IV were to be considered as a hybrid resulting from unions of Groups II and III, crosses of Group IV would always result in children in Group II, Group IV, and Group III. In sufficiently large families the groups would be distributed numerically so as to maintain the relationship of one Group II, two Group IV, and one Group III. Crosses of Group IV may result in only Group IV children. There is no way by which a union of *A* and *B* can explain the origin of Group IV. The conclusions of Moss in reference to the existence of three specific iso-agglutinin combinations, *A*, *B*, *C*, in the serum, and three distinct receptor substances, *a*, *b*, *c*, in the red blood cells, as arranged by that author into four groups comply exactly with data obtained in my study of the germinal transmission of the blood group to subsequent generations. The constitution of each blood group is specific whether present in the blood or represented by a determiner in the germ plasm. Any variability in the hypothetic structural formula for a blood group is untenable. There are four blood groups known today and, as the theory of heredity is based on the belief of a specific determiner for each hereditary character, transmissible through the germ plasm, I believe in the existence of four separate and distinct biologic determiners for the blood groups.

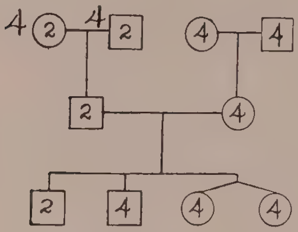

FIG. 219.—Transmission of blood Groups II and IV through three generations and the occurrence of twins of the same blood group.

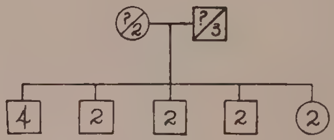

FIG. 220.—Crossing of blood Groups II and III. The result demonstrates the inability to determine parentage from a two generation study of the blood group.

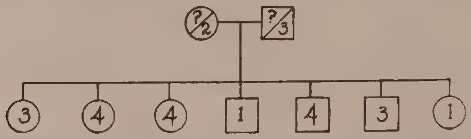

FIG. 221.—The frequency of additional groups besides those represented in parents is due to scarcity of pure Group III and the frequency of heterozygous Group II.

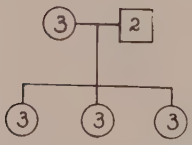

FIG. 222.—Demonstrates the necessity for at least four children for the study of the segregation of characters.

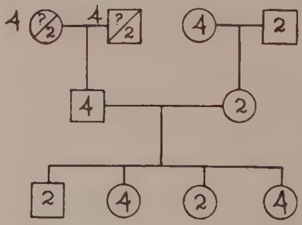

FIG. 223.—Transmission of blood Groups II and IV through three generations demonstrating the heterozygous nature of one of the parents on the left in the parental generation.

The whole story of the origin of the blood group is not told in the blood of the parents of a family, and the fact must ever be kept in mind that ovaries and testes are the vehicles through which past and present biologic characters of man are linked together. If the function of germinal tissues to segregate and transmit characters to subsequent generations is ignored, worthless hypotheses and formulas will be established in order to explain an evident character occurring in man. A curious situation would exist in the family represented in Figure 226 if the criteria of Ottenberg were accepted. The twins were in different groups, and one was in a group different from that of either parent. The danger of drawing conclusions from two-generation studies is shown in Figures 218 to 222. Such families are without conclusive value in the study of the inheritance of the blood group (Figs. 224 and 225) and dangerous when utilized as criteria to establish the usage of the blood group in medicolegal affairs. There are more than 200 small families or parts of families on record at the Mayo Clinic.

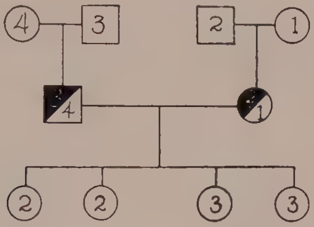

FIG. 224.—If this family had been grouped through two generations only, it could be believed that the resulting groups were simply the product of a rearrangement of specific substances *A* and *B*, and *a* and *b*. A review of an earlier generation gives the clue to the groups to be expected in subsequent generations. The blood of parents in the second generation was in Groups IV and I, but all four groups were present in the germ plasm. The dormant characters reappeared, and it must be admitted that the evident characters would have appeared had the family been sufficiently large to permit of segregation of all the determiners for blood group in the germ plasm. If not, blood group is not hereditary. An attempt to state that unions of Groups I and II, and Groups I and III can only give rise to similar groups is to ignore the possible heterozygous state of a parent. Unions with Group IV or of Groups II and III give rise to all groups because persons who are pure for the common groups, Groups II and IV, are very difficult to find, it is still more difficult to find persons who are pure for the rare groups, Groups I and III.

Alexander, in 1921, made an investigation in order to determine if Mendel's second law was fulfilled in the transmission of blood group. He came to the conclusion, in malignancy in particular, "While persons belonging to all four groups are liable to malignant disease, those in

Groups I and III appear to be peculiarly susceptible, and the clinical type of disease is, generally speaking, more malignant." He believed this situation arose by linkage of the factors for cancer and for blood group. The investigations of Higley and myself on material collected by Sanford in the Mayo Clinic showed this conclusion to be incorrect. In a study of 2,446 persons with various diseases we found that there were no evidences of linkage. There was no evidence that a person in a particular blood group was more susceptible to a certain disease and the reactions to disease were practically the same in all blood groups.

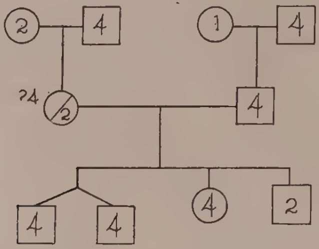

Fig. 225.—In this family three groups were crossed in the first generation. The members of the second generation showed only one group in their blood and unless the blood group of the third generation is studied, there is no way of determining the heterozygous or homozygous nature of the parents in the second generation. If the numerical superiority of one character to another is a fixed thing in man, either Group II or Group IV should constantly recur in greater numbers when they are crossed. Other families studied indicate that Group II appears with greater frequency when crossed with Group IV. The female of the second generation may have Groups II and IV in her germ plasm, but at present this cannot be proved.

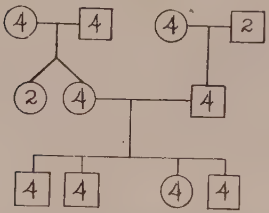

Fig. 226.—Segregation of pure blood Group IV from the parental generation as shown by all the children being in the same group. The twins are in different groups which demonstrates the heterozygous nature of one parent, and the peculiar segregative power of the germ plásm.

The percentage relationships of the blood groups in the two sexes did not vary in any way in 2,176 groupings of 1,245 males and 931 females. The percentage distribution in the males was Group I, 3.69 per cent; Group II, 40.97 per cent, Group III, 9.39 per cent, and Group IV, 45.77 per cent. In the females the distribution was Group I, 3.97 per cent; Group II, 41.46 per cent; Group III, 8.69

per cent, and Group IV, 45.85 per cent. The families represented in Figures 206 to 226 demonstrate the transmission of the blood group between males and females without regard to sex. There are no evidences of sex linkage in the transmission of the blood group.

The second law of Mendel, namely, the independent assortment of characters, so far as data at present are concerned, is fulfilled by the blood group.

Comment.—The blood group is an expression of an hereditary character of man. There are four characters known at present which are arbitrarily designated Group I, Group II, Group III, and Group IV. The blood group is transmitted by the germ plasm according to the first and second laws of Mendel. The hybrid stage is absent.

Whether the Jansky or Moss classification is used in this study of the inheritance of the blood group is not of importance. The groups may be classified by either method and are transmitted between generations in accordance with the same rules. There is no method available at this time by which a strict or presumptive delimitation of the blood group possible in children resulting from the union of two persons can be made. Careful investigation conducted into the ancestry of every generation must be carried out in order to ascertain the blood group possibilities in any family, and even then the medicolegal application of blood groups will be surrounded with many difficulties.

The blood group offers a concrete means for the study of heredity in man.

INHERITANCE OF MIGRAINE: STUDY II

The demonstration of the transmission of migraine through generations by means of the germ plasm transfers the condition from the category of disease to that of biologic character of man. The term "migraine" designates an unknown physiologic process which is recognized by periodic attacks of pain, usually in the head, either unilateral or bilateral, but occurring also in the abdomen, and in either location frequently associated with nausea, vomiting, mental depression, visual phenomena, and many vague somatic disturbances. One or all of the symptoms may occur in an attack, which lasts from a few to several hours or days. The first expression of the character appears early in life, and, as a rule, the manifestations disappear during the fourth decade.

Studies instituted to prove migraine expressive of an hereditary character must of necessity include the investigation of parents and at least four children in families in which there were unions of a person with migraine to a person without migraine, of known heterozygous persons, or of two persons with migraine. "Without migraine" is the contrasted character. Under like conditions, the segregation of the character will occur among the children in a fairly definite manner.

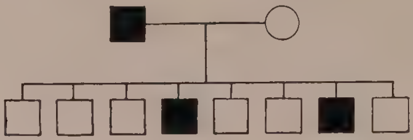

FIG. 227.—The segregation of the migraine character in families in which a person with migraine and a person without migraine have been crossed.

The distribution of migraine in families.—A study was made of 127 families one or more representative of which were examined in the Mayo Clinic in 1919. Migraine followed the two laws of Mendel (Figs. 227–229). Of the total number of children in the 127 families, 198 had migraine and 610 had the character, without migraine. At the time the study was reported a combined mendelian ratio was calculated for all the families studied. This ratio was incorrect, as amalgamation of the crosses was contrary to the scheme of Mendel. The ratios were correct for the individual groups. The same difficulties exist in working out a mendelian ratio for migraine as exist for the blood group.

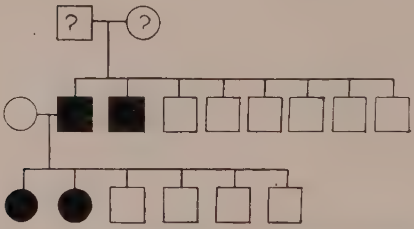

FIG. 228.—The value of searching for all the evidence available in a family in which one member has migraine. It can be presumed that a parent in the first generation had migraine because of the distribution in the second generation. The segregation is carrried into the third generation.

Like all hereditary characters migraine exists in either the homozygous or the heterozygous state. The heterozygous state (Fig. 230) has led many writers to say that migraine is hereditary in 90 per cent of instances and in various other percentages, because it occurs in a number of families in which it is not demonstrable in the parents. During the last two years many cases in the Mayo Clinic have been observed, in which migraine was not present in the parents, but present in the brothers or sisters, if the family was sufficiently large, or present in one or the other of the grandparents. Data derived from patients having no knowledge of their parents and grandparents is not usable as evidence for or against the mendelian transmission of migraine. Such information is valueless on either side of the question. It is to be remembered that by means of the heterozygous status of certain persons a character may be transmitted through many generations of small families without any signs of its presence. The character may appear in the first large family.

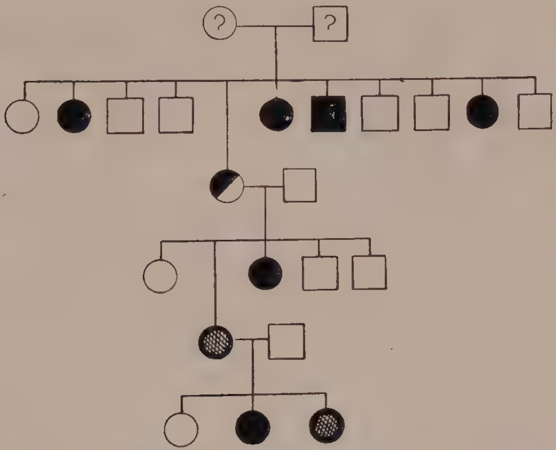

FIG. 229.—Transmission of migraine with abdominal crises.

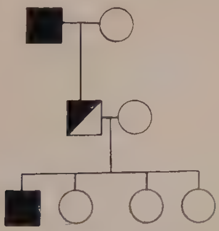

FIG. 230.—The heterozygous status of the male of the second generation as shown in the reappearance of the character in the final generation.

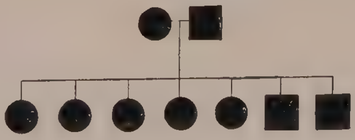

FIG. 231.—Cross of persons with the pure migraine character.

The homozygous state of migraine has been studied in three families in which both parents had migraine. If migraine exists in a homozygous state, all children resulting from such unions should have migraine. This occured in the three families studied (Figs. 231–233). Although this is an interesting observation, the data are too meager to be of value in determining if the relationship of the dormant and evident phases of migraine are reversible. It may be that a person with migraine may become the parent of children without migraine, just as it has been shown that the relationships of the blood group in the heterozygote are reversible. This subject requires careful study.

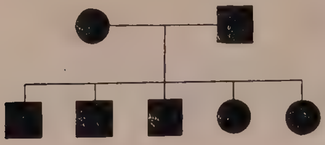

Fig. 232.—The union of homozygotes results in all offspring having the same character.

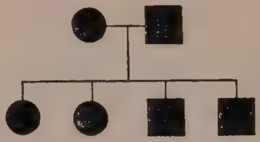

Fig. 233.—If migraine is heterozygous, for without migraine individuals without the character should be segregated in families of four or more children. The absence of such segregation is illustrated in this family.

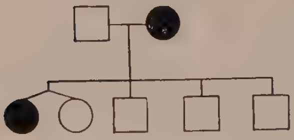

Fig. 234.—The segregative power of the germ plasm. One twin and migraine, the other was without migraine.

One family has been studied (Fig. 234) in which there were twins; one had migraine and the other did not have migraine. This is interesting when compared with the appearance of different blood groups in twins (Fig. 226).

In the description of the causal factors for a number of diseases, various writers have given migraine as one of the etiologic factors. So far as is known, the determiner in the germ plasm for migraine has nothing to do with the production or evolution of any character other than itself. The migraine determiner is as specific for itself as the determiner for a particular blood group is for itself. Any disease may occur in the person with migraine. It is an association and not an etiologic relationship.

Comment.—Migraine is the expression of an hereditary character, but the physiologic processes which occur at the time of the manifestation of its phenomena are unknown. It is not possible to change the blood group by either surgery or drugs, so it does not seem reasonable to expect that migraine which is a similarly derived character could be influenced by any of the procedures recommended. Patients with migraine who have been examined in the Mayo Clinic demonstrate the futility of all sorts of treatment. Evidence has not been accumulated to substantiate the belief that a "tendency to migraine" is inherited; "migraine" and "without migraine" are the inheritable characters. A person either has or does not have migraine, just as a person always belongs to a blood group.

INHERITANCE OF ESSENTIAL EPILEPSY: STUDY III

There is no gross pathologic basis for the explanation of the seizures of essential epilepsy. It is characterized in man by periodic seizures in which there is loss of consciousness, preceded by more or less marked prodromal sensations, and followed by and associated with tonic or clonic spasms of the general musculature. The seizures last from a few minutes to one hour or more, and their frequency is variable. A seizure in which there are severe convulsions and loss of consciousness is termed "grand mal." A milder form in which vertiginous or momentary blank sensations replace the convulsions is termed "petit mal." Hippocrates believed that essential epilepsy began in utero, and as a consequence of this belief and the absence of a pathologic basis, many diseases, such as neurasthenia, hysteria, insanity, and the undefined group of diseases known as nervous disorders or neuropathies have been incriminated as causal agents. St. Hildegard seems to have been one of the earliest writers to suspect that migraine and essential epilepsy were expressive of the same entity.

The relationship of migraine to essential epilepsy.—In order to obtain data on the relation of the various neuropathic influences to essential epilepsy, two series of cases observed in the Mayo Clinic were analyzed. The results warranted the dismissal of all of the so-called nervous disorders as related factors, since they occurred not more often in the ancestral history of persons with essential epilepsy than in the ancestral history of persons with diseases of known etiology. Migraine is the only character which appeared with enough frequency to attract attention. In the first series of 127 cases migraine occurred in the ancestral or personal history or in that of the brothers and sisters in 53.9 per cent of the cases. The 127 cases comprising the second series had been carefully studied in the Section on Neurology of the Clinic, and of these cases 66.4 per cent gave a history of migraine in ancestors, brothers or sisters, or in the personal history. In the former series migraine was present before the onset of essential epilepsy and alternated with or continued with epilepsy in 14 per cent of the cases studied. In the latter series this occurred in 10.5 per cent of the cases. The genetic relationship of migraine to essential epilepsy seemed to be quite striking.

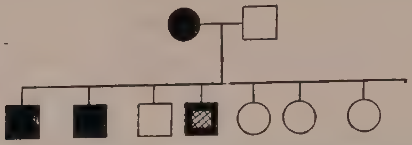

FIG. 235.—The failure of essential epilepsy to disturb the numerical relationship of normal persons to those with the inherited character. Essential epilepsy is superimposed on an individual with the migraine character.

The familial distribution of migraine-epilepsy character.—If essential epilepsy is expressive of the same underlying biologic factor on which migraine depends, its appearance in families would not disturb the relationship of persons with migraine to persons without migraine; it would simply replace or alternate with the migraine character in certain persons. The same laws and requirements that govern the transmission of the blood group or migraine alone would be followed and fulfilled.

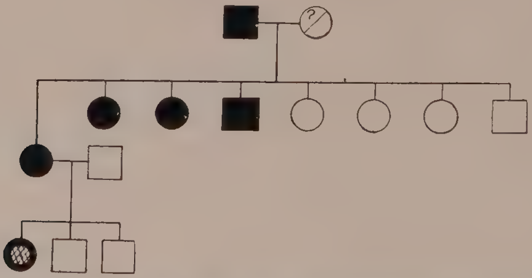

FIG. 236.—The number of persons in the second generation with migraine is greater than is to be expected from a cross of a pure migraine with a pure normal. This has been observed in several families and is considered due to the heterozygous, although unproved, status of the apparently normal parent. The character appears as essential epilepsy in the final generation.

Essential epilepsy on empirical grounds was considered as simply another phase of the phenomena of the migraine character in a study of forty-seven families whose histories where complete for ancestral data. The contrasted character was "without migraine-epilepsy," or what is commonly called the normal. The same segregation of characters was seen as when considering migraine alone (Figs. 235–237). At a subsequent date thirty-five similar families were studied, and the data obtained in the first families were altered in no way. In a certain number of the patients studied, varying in all series from 10 to 14 per cent, migraine and epilepsy alternated irregularly.

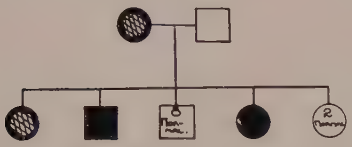

FIG. 237.—The mother had epilepsy in early life, replaced by migraine. The same segregation of the characters occurred as if the mother had always presented migraine.

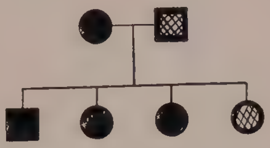

FIG. 238.—The crossing of a migrainous person with an essential epileptic person. The character, epilepsy, behaves as does the character, migraine.

If essential epilepsy is expressive of the same phenomena as migraine, the marriage of an epileptic person to a migrainous person would result in all of their children having migraine or all or part having essential epilepsy. One family has been found to fulfill this condition; all the children had migraine, and in one the migraine alternated irregularly with epileptic attacks (Fig. 238).

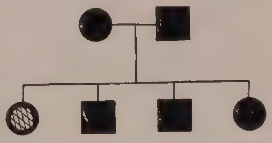

FIG. 239.—The results of crossing two persons with migraine.

If essential epilepsy depends on the factor of migraine for its evolution, the marriage of homozygotes or heterozygotes for migraine should result in the production of a certain number of children subject to seizures of essential epilepsy. The marriage of two persons with migraine is quite rare, and as a consequence the opportunity to observe the frequency with which a child with essential epilepsy should result from such unions would be very infrequent. I have found only one family (Fig. 239) which furnished any information on the subject in the files of the Mayo Clinic. Many families (Figs. 240 and 241) have been found which demonstrate the heterozygous property of the normal to transmit migraine, essential epilepsy, or both to their children, because of the strain which had been introduced into their germ plasm by the grandparents.

Comment.—Essential epilepsy and migraine are transmitted from generation to generation as the expression of the same underlying factor in the germ plasm. The mechanism for the production of the seizures is unknown. The organic factors capable of producing phenomena similar to those of essential epilepsy are so numerous that the classification of an individual in the class with essential epilepsy demands extreme caution.

A diminution in the number of essential epileptics by segregation in colonies is not be to hoped for, as the person with migraine is more likely to produce epileptic offspring than the epileptic person himself.

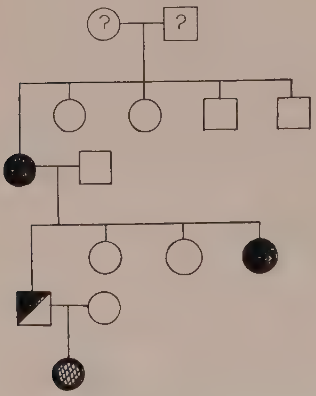

FIG. 240.—The transmission of the migraine-epilepsy character because of the heterozygous status of the male parent.

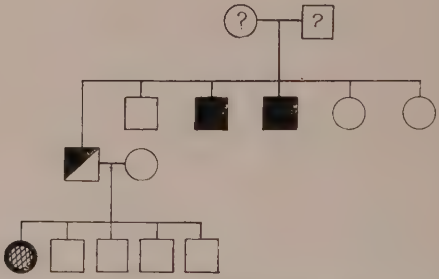

FIG. 241.—The heterozygous status of the germ plasm and its segregative power. The final generation studied would have no value if considered by itself without information obtained from other families.

The theory that essential epilepsy and migraine are the expression of a biologic character, and their manifestations are, therefore, physiologic, needs offer no insurmountable obstacles in its acceptation. If it is possible for such striking characters as waltzing in a mouse and tumbling in a pigeon to be hereditary, there is no reason why characters equally striking might not appear in man. The management of migraine and essential epilepsy as expressions of biologic characters undoubtedly will result in a greater degree of happiness and health than has hitherto been possible for those individuals because of the unlimited and ever-varying type of operation and drug therapy which has been carried out without benefit.

DIABETES MELLITUS: STUDY IV

From the earliest history of diabetes mellitus references have been made to heredity as an explanation for the occurrence of a varying percentage of cases of the disease. The reported families were compiled, in 1912, by Foster, who at the same time reported a family observed by himself. In practically all of the articles on the subject mention is made of the number of persons in the family who were afflicted, but no mention is made of those who were in good health. The three families reported by Long are noteworthy exceptions. Von Noorden, Naunyn, May and, more recently, Allen have called attention to the importance of heredity in diabetes. Allen suggests that the subject should be studied by the methods used by biologists in determining hereditary characters, as no attempt has been made to study the condition in the light of the laws of heredity.

If diabetes mellitus is to be considered as representative of a unit character, it would be interpreted as a physiologic expression of a cycle in the life of certain persons, whereby they would lose the power to metabolize carbohydrates and as a consequence a portion or all of the sugar ingested, the stored carbohydrates, and a portion of the body protein and ingested protein are converted into sugar and excreted as such in the urine. At the same time the chemical changes which result in coma and death would be the final expression of this lethal cycle. The contrasted character would be what is called "normal," or that possessed by a person whose carbohydrate metabolism is constituted so that the phenomena of diabetes mellitus do not appear. The families should be studied through two generations, and at least three and preferably four children should be present in the families used for study.

Diabetes mellitus not a mendelian character.—Diabetes mellitus, if hereditary, must conform to the known laws of heredity. To determine if such be the case the progeny of persons with diabetes mellitus married to persons without diabetes mellitus have been studied. The material consisted of thirty-four families, seventeen of which were studied through two generations and seventeen through three generations. The total number of diabetic offspring was sixty-five; 274 were without any evidence of diabetes mellitus at the time the data were collected. Sixty-five children (16.08 per cent) died in early life.

The results of unions (Figs. 242–244) of diabetics (homozygotes) and nondiabetics in the cases studied revealed no information to show that the condition was transmitted through the germ plasm. The occurrence in the children did not conform to the mendelian laws. Further investigation in these same families may reveal information of great value.

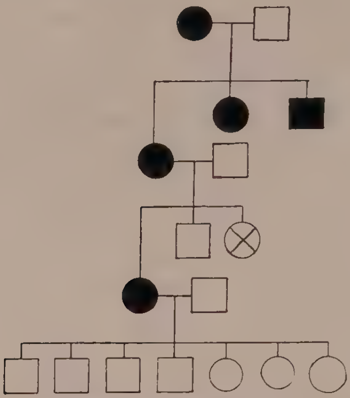

FIG. 242.—A family in which diabetes mellitus has occurred for three generations. It appeared in the mother of the last generation at the thirty-third year. None of the children was affected at the time the patient was investigated.

Occasional families have been observed (Fig. 245) which suggested the possibility that diabetes mellitus might be transmitted to a subsequent generation because of the heterozygous state of a parent. A study to throw definite light on this subject was made in eighteen families, of which eleven were studied through two generations, and seven through three generations. There were eighteen children with diabetes, and 126 without. Thirty-five of the children (19.05 per cent) died in early life. The impression that diabetes might be transmitted

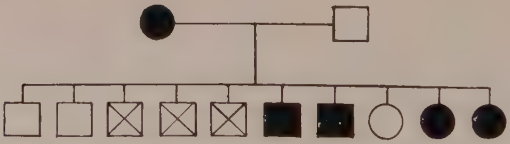

FIG. 243.—The results of crossing the diabetic and nondiabetic persons. The number of diabetic offspring is too large, as the father's family was free from diabetes. Three children died in early life, presumably free from diabetes mellitus.

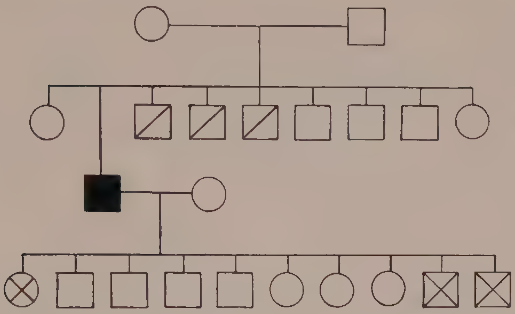

FIG. 244.—The failure to conform to known laws of heredity is shown in this family. Diabetes if hereditary would have appeared at the age of sixty-two or thereabouts in at least two children in the second generation.

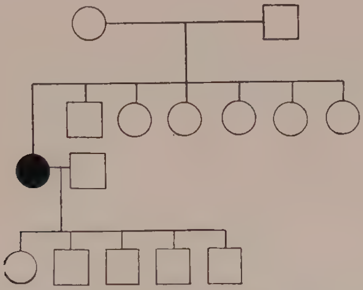

FIG. 245.—This family suggests that diabetes mellitus might be transmitted through the germ plasm because of the heterozygous nature of the male parent of the second generation.

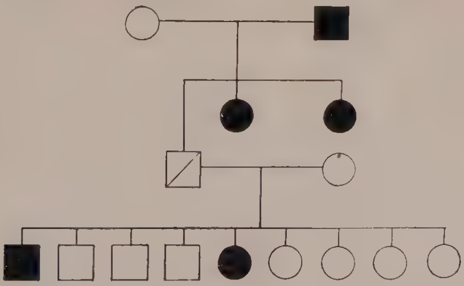

FIG. 246.—A family illustrating the families studied to determine if diabetes mellitus is transmitted by a heterozygote.

through the germ plasm on account of the heterozygous nature of a parent was not supported by the data obtained from the eighteen families studied. These families are typified in Figure 246.

If diabetes mellitus were hereditary, homozygous and heterozygous individuals would result from the crossing of a diabetic person with a nondiabetic. The failure of the homozygous principle to be supported has been shown in the cases of diabetes reported by Crofton and others in which it has been found that both parents may have diabetes mellitus and none of the children be afflicted. The lack of conformity to the laws of dominance and recessiveness in man because of the absence of the hybrid stage may explain certain discrepancies in the familial occurrence of diabetes, but neither the homozygous nor the heterozygous principles in heredity have been fulfilled by diabetes mellitus.

Method for collection of data.—The methods used today for the collection of data in families where diabetes mellitus occurs are not such as will ever result in obtaining data of conclusive value. To prove diabetes mellitus hereditary, a cyclic nature of the disease would have to be postulated, that is, the condition would make its appearance at approximately the same age and have a definite progress in a certain number of the members of the family. Therefore, data should be obtained in each family concerning: (1) the time of onset in the parents, (2) the number of brothers and sisters of the parents and the age of each, (3) the age of each at onset of diabetes, (4) the number of children in the last generation, (5) the age of each child when the condition appeared, and (6) the ages of those at or beyond the age at which it appeared in the parents. The collection of the data would necessitate a follow up system of investigation and a study of the children as they arrived at the proper age. In no other way will it be possible to prove that conditions like diabetes mellitus should be transferred from the status of a disease to the list of conditions in man which are expressive of a biologic character transmissible through the germ plasm. The data presented in my study did not fulfill these requirements. So far as the data collected are reliable, there is not the slightest evidence to justify the statement that diabetes mellitus is at times hereditary. There is also insufficient evidence to show that the condition is not hereditary, but the evidence does point more toward the quantitative action of some causal factor than to the expression of the segregative properties of the germ plasm.

The high mortality in early life of children born of diabetic parents is striking.

ESSENTIAL ASTHMA: STUDY V

In essential asthma, as in all conditions in man, the etiology of which is obscure, the mechanism of heredity has been believed to play an etiologic rôle. Geddings reviewed the statistics of the earlier writers, and came to the conclusion that the tendency to essential asthma is hereditary. All of the earlier writers, with the exception of Drinkwater, reported a percentage of inheritance of essential asthma varying from 10 to 50 per cent. Drinkwater reported his families as expressive of the segregative power of the germ plasm. The more recent literature has been reviewed by Adkinson, who at the same time presented data obtained from a large number of cases. She found a family history of essential asthma in 48 per cent of the 400 cases studied, and came to the conclusion that asthma is hereditary in a varying percentage of cases. She also concluded that asthma appeared at an earlier date in the children than in the parents. If asthma is an hereditary character it must have been present in man since his appearance on earth, as there is no way for hereditary characters to be kept extant except by breeding of those in whom the character is present. The known period of man on earth has been computed to be millions of years. Essential asthma was distinguished as a distinct clinical entity by Willis about 1600. If a character were present in primeval man, or even since 1600, and appeared at a perceptibly earlier age in the children of each generation, the cycle required for its appearance would eventually be brought down to a period earlier than the preformation of the embryo, or in the germ plasm, and after it had arrived at that state would of necessity either have to disappear, or by some miraculous process again revert to appearance in old age. This claim is made for other conditions in man, but there is no evidence in heredity to support such an hypothesis.

An investigation to demonstrate the transmission of essential asthma to subsequent generations by the germ plasm must be conducted in the same manner as that for migraine. It would be transmitted in exactly the same manner and follow the same rules of heredity. For this reason a small number of families would be sufficient to establish the hereditary character of the condition. The contrasted character would be "without asthma."

The families presented in Tables 1 and 2 are sufficient to justify a conclusion in regard to the hereditary nature of essential asthma. In families used for the study the children had reached the age at which the condition appeared in the parent. In the seventeen families in

TABLE 1

Transmission in Seventeen Families in Which Father or Mother Had Asthma.

Asthma in	Children	
	With asthma.	Without asthma.
Mother	1	14
Father		5
Mother	2	7
Mother	1	4
Mother	1	3
Mother	1	8
Mother		6
Father		4
Father		4
Mother		3
Father		5
Mother		8
Mother		9
Father		5
Mother	2	6
Father		7
Father		4
	—	—
	8	102

TABLE 2

Transmission in Thirty-nine Families in Which Neither Father Nor Mother Had Asthma.

Children					
With asthma.	Without asthma.	With asthma.	Without asthma.	With asthma.	Without asthma.
1	7	1	5	1	12
1	7	1	7	2	3
1	3	1	6	1	4
1	3	1	5	1	5
1	7	1	9	2	3
1	4	1	4	1	5
2	3	1	6	1	5
1	3	3	4	1	6
1	3	2	12	1	5
1	12	1	6	1	5
1	6	1	7	1	7
1	3	1	8		
1	9	2	4	—	—
1	9	1	4	46	226

Table 1 there was evidence of asthma in parent and offspring. This does not warrant the conclusion that asthma is hereditary. The law for the segregation of characters is not followed to a degree in any way approximating the numerical ratio for hereditary characters. In

Table 2 the data presented does not lead to the conclusion that asthma was transmitted in these families as a result of a heterozygous state of one or the other parent. If a character or condition under consideration does not follow the course of either the homozygous or heterozygous type for hereditary characters, it is safe to conclude that the condition is not hereditary. The study of a larger group of similar families would show the same figures.

Comment.—Essential asthma in its familial appearance follows none of the known laws of heredity. It is not the expression of a specific hereditary biologic character of man.

PROTEIN SENSITIVITY: STUDY VI

Protein sensitivity has been attributed by Osler, Oppenheimer and Gottlieb, Walker, Longcope, Barber, Cooke, and others to the inheritance of a particular type of sensitive cells which react in a particular way when subjected to the influence of various protein substances. This belief permits of a very important investigation in man.

For many years "the inheritance of susceptibility to certain states" has been believed. If such be the case, the susceptibility must be transmitted in accordance with the laws which govern the inheritance of all characters. The mating of a person with protein sensitivity to a person without protein sensitivity, if the condition were dependent on the transmission by the germ plasm of a particular type of cellular protoplasm, would result in the production of a certain number of children of this susceptible type, some of whom would be heterozygous, others homozygous. If the children of such crosses were exposed to the same conditions of protein influence, and they would be, so long as they lived under the same climatic and seasonal environments, those who inherited the peculiar type of somatic cells would react to the foreign substance in such numbers as to fulfill the mendelian law for the segregation of characters. The possibility of the inheritance of a type of cellular structure that is susceptible to certain influences could be demonstrated under no more propitious circumstances.

The familial occurrence of protein sensitivity.—In order to investigate the possibility of inheritance of the susceptibility to foreign protein, I have studied a small number of families in which there was parental protein sensitivity, and a larger group in which there was no parental sensitivity to proteins.

The number of families studied in Table 3 is very small, but the segregative property of the germ plasm does not wait until the hundredth family. The segregation will appear in the first family studied as well as in the last. There is no evidence in these families that the germ plasm carried any factor on which the protein sensitivity depended.

The twenty-four families of Table 4 consisted of twenty-eight children with protein sensitivity and 126 without. The families might be considered as expressive of the transmission of the condition by a heterozygous parent. This assumption is disproved by the failure of protein sensitivity to reappear in the third generation of certain families of Tables 3 and 4. Hereditary characters are carried on forever, otherwise the theory of germinal continuity would be false, and there is no obvious

TABLE 3

THE FREQUENCY OF PROTEIN SENSITIVITY IN CHILDREN OF SEVEN FAMILIES WHEN PRESENT IN ONE PARENT.

Protein sensitivity in	Children	
	With protein sensitivity.	Without protein sensitivity.
Mother	1	3
Mother		6
Mother	1	11
Mother		4
Mother		4
Father		4
Mother		4
	2	36

TABLE 4

THE FREQUENCY OF PROTEIN SENSITIVITY IN CHILDREN OF TWENTY-FOUR FAMILIES WHEN ABSENT IN PARENTS.

Children					
With protein sensitivity.	Without protein sensitivity.	With protein sensitivity.	Without protein sensitivity.	With protein sensitivity.	Without protein sensitivity.
1	5	1	6	1	7
1	4	1	6	1	5
1	9	1	3	1	5
2	2	2	5	1	4
1	4	2	2	1	3
1	3	1	3	1	6
1	5	1	6	1	5
1	9	1	7	1	6
				28	126

reason why an exception should be made in the case of protein sensitivity.

Comment.—A consideration of the families represented in Tables 3 and 4 leads me to the conclusion that protein sensitivity is not dependent on the transmission through the germ plasm of a factor which is responsible for the appearance of the condition in man. Furthermore-the data presented are criteria against the continuation of the use of the expression, "inheritance of susceptibility to disease." No evidence has been presented in the study of heredity to show that characters are susceptible of appearing or that there is a tendency for them to appear. They are either present or absent. There is no uncertainty.

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THE GROWTH OF THE ORGANS AND SYSTEMS OF THE SINGLE COMB WHITE LEGHORN CHICKEN*

HOMER B. LATIMER

One hundred seventy-four single comb white leghorns from the regular stock, and hatched in four different lots by the Poultry Department of the University of Minnesota were used in this study. The increase in gross body weight for each chicken was studied for two hundred eighty days. Ninety-four of the 174 chickens ranging in age from day of hatching to three hundred days were necropsied and the growth in weight of the various organs and systems was determined. Six older chickens were taken from the regular stock for comparison, making a total of 100 chickens necropsied. Fifteen subnormal chickens were necropsied and these will be reported on later.

The chickens were killed with chloroform. The gross body weight, the length of the body (beak to anus), head, leg, wing and the dorsoventral and transverse diameters of the thorax were obtained. The head, skin, feathers, comb, wattles, ear lobes, skeletal muscles, ligamentous skeleton, entire digestive tract (with contents), and parts separately and without contents (stomach, gizzard, and intestines), yolk sac, liver, pancreas, trachea and lungs (together), heart, thyroid, thymus, spleen, suprarenals, hypophysis, kidneys (right and left together), ovary, oviduct, testes (separately), brain, spinal cord, and eyeballs were weighed. No record was made of the weight of the blood, fat, mesenteries, and larger vessels and nerves. Care was taken to prevent drying and all the smaller parts were weighed in closed containers on a chemical balance sensitive to a tenth of a milligram. For the entire chickens and the larger parts, a laboratory balance sensitive to a tenth of a gram was used.

The weight of each system and organ was reduced to a percentage of the net body weight, or the gross body weight minus the contents of the digestive tube. The gross body weight, the six linear measurements, the growth of the thymus, ovaries, and oviduct were plotted on age in days as abscissæ, and all the other parts were plotted on gross body weight. Empirical formulas were determined for all the resulting growth curves except the parts of the reproductive tract, comb, wattles, and ear lobes. The more important findings may be summarized as follows:

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* Abstract of unpublished thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1921. From the Department of Anatomy, University of Minnesota, Minneapolis.

The curve of postnatal growth of the entire body of the chicken shows three general phases: (1) a period of slow growth, including a brief postnatal decrease in weight; (2) a period of rapid (pubertal) growth, during which a sex difference in body weight begins, and (3) a period of slow increase in weight.

The weight of the head shows a marked sex difference due apparently to the larger development of the comb and wattles in the male.

The growth in weight of the skin (excluding the feathers) is directly proportional to that of the entire body, forming about 9 per cent of the net body weight. The feathers increase in both absolute and relative weights to just before sexual maturity. Then follows a decrease in absolute and relative weights, the growth curve thus somewhat resembling that of the thymus.

The skeletal muscles increase from 21 or 22 per cent at hatching to a little less than 50 per cent of the body weight in the adult.

The skeleton at first grows a little less rapidly than the entire body; it forms 11 per cent of the body weight in the mature male and 8 per cent in the female. The weights and linear measurements show that the female skeleton matures earlier than the male.

The digestive tube and its regions, stomach, gizzard and intestines, and also the pancreas, all grow at about the same rate, showing a short initial rise in relative weight, followed by a slow decrease in rate of growth up to maturity. The empty tube reaches a maximum of 18.5 per cent of the body on the sixth day, decreasing to about 5 per cent in the adult. The weight of the contents of the digestive tube is extremely variable. The yolk sac was found in all chickens necropsied, with one exception, to and including the thirty-eighth day, and thereafter often to the two hundred thirty-seventh day. Meckel's diverticulum is constantly present.

The liver decreases from an early maximum of 6.2 per cent of the body weight to about 2.5 per cent in the adult. Its weight increases markedly in the older chickens, particularly in the fat females.

The weight of the lungs and trachea is variable and shows an apparent sex difference in the older chickens, being heavier in the males.

The heart shows a marked growth in absolute and percentage weights during the later part of the period studied, or beginning at about 1,400 gm. gross body weight.

The thyroid grows more slowly than the entire body, thus forming a curve concave superiorly. The percentage values are variable, with a marked decrease from 200 to 400 gm. gross body weight.

The thymus increases in percentage and absolute weight to sexual maturity and then undergoes involution, decreasing in relative and absolute weight. Its changes are more closely related to age than to body weight.

The suprarenals and hypophysis are somewhat variable in weight, but neither shows a sex difference.

The kidneys show a marked initial rise from 0.6 per cent on the day of hatching to 2.0 per cent of the net body weight at five days, followed by a slow decrease to about 0.6 per cent in older and adult chickens.

The ovary, oviduct, testes, and comb and wattles are all extremely variable in weight. They all tend to form a four-phase curve of growth, with a marked acceleration at puberty.

The brain, spinal cord, and eyeballs increase rapidly at first, followed by a slow growth later. The relative (percentage) weights of these organs show no initial rise, but decrease progressively from time of hatching.

THE SERUM PROPHYLAXIS OF MEASLES*

MORLEY D. McNEAL

The highest mortality from measles occurs during the first six years of life, particularly among those who are physically below normal. As it is difficult to eliminate exposure, it is important to have some method whereby the disease can be prevented or the severity of the attack diminished during the period of danger, especially among those whose resistance is lowered by malnutrition and chronic disease. About one year ago Degkwitz, of Munich, reported the successful preventive inoculation with serum from convalescent patients of 172 children exposed to measles. His methods have been carried out to a large extent during a recent epidemic of moderate severity in Rochester. The donors were free from syphilis and tuberculosis and had gone through fairly severe attacks of the disease without complications or sequelæ. They were bled after intervals of five, seven, or nine days following defervescence. After varying periods subsequent to exposure, between three and seven days, 5 c.c. of serum was injected into the muscles of the thigh.

The sixteen children so inoculated had never had measles, but had come into intimate contact with patients in the contagious period, so that the disease was expected to develop. Twelve of the sixteen children remained well and four developed measles, but of an extremely mild type. The catarrhal and constitutional symptoms were very moderate and the rash was exceedingly sparse. In three of these four patients the incubation period was lengthened to nineteen days. These failures to immunize the patient were perhaps due to a combination of a more overwhelming infection and the employment of serum obtained too early from the donors. One child, who was inoculated on the fifth day of incubation, remained free from measles until two months later, when he developed a fairly severe attack of the disease. This suggests that the immunity in some cases does not persist for more than sixty days.

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* Abstract of paper published in full in the Journal of the American Medical Association, 1922, lxxviii, 340–341. From the Section on Pediatrics, Mayo Clinic.

The nature of the immunity is not clear. The fact that the serum is most effective when obtained from the donor seven days after the disappearance of fever suggests a passive immunity, because at that time a maximum number of antibodies would be expected. The short period of protection also argues in favor of a passive process. Degkwitz, however, reported that serum removed from persons several months after successful inoculation, performed as late as the sixth day of incubation, protected children who had been exposed. This suggests that as early as the sixth day after infection active allergic reactions have occurred in the organism.

Degkwitz's method recommends itself most highly for the prevention of measles during the period of danger between the fifth month and the sixth year, in tuberculous children, and in those physically below normal. The method would be of great value in institutions where large numbers of frail children are intimately associated. The marked attenuation of the disease with permanent immunity, but without complications or sequelæ, seems to be just as favorable, if not more favorable, a result as absolute, but transient protection.

GRADUATE MEDICAL EDUCATION: EXPERIENCE WITH THE MINNESOTA PLAN*

E. P. LYON

Medical specialism is indispensable and the training of specialists is of vital importance alike to the medical profession, to the general public, and to the state. I propose to discuss the question of the education of specialists in general, and then tell you what we are doing as regards medical specialists at the University of Minnesota.

Let us note first how specialists are trained and tagged in some other professions.

Consider first the profession of college teaching. If you examine the faculty list of any of our great colleges, you find that most of the active professors have the letters "Ph.D." following their names. Others are masters of arts or science. There are doctors of philosophy in chemistry, physics, and the other natural sciences; in history, economics, and sociology; in language and literature. Just what does this degree mean?

First, you may be sure that in almost all cases the Ph.D. is an earned degree.

Second, you may be sure that before he started to earn his Ph.D. the student had a fair preparation, as evidenced by a bachelor's degree.

Third, the Ph.D. means that the possessor worked for three years or more on the particular subject for which the Ph.D. was awarded. It means that he also acquired a thorough working knowledge of related subjects. If he is a Ph.D. in Chemistry, he did considerable work in Mathematics and Physics, because without these he cannot know Chemistry. The Ph.D. indicates, to use our familiar word, that the holder is a "specialist" in some field of knowledge.

Fourth, the Ph.D. connotes something which is of special interest to you, because there is a feeling among doctors of medicine against that word philosophy. They think that the Ph.D. implies impractical theorizing, a detachment from the world and the world's affairs. Some men, it is true, may be impractical and detached; but it is not their degrees that makes them so. On the contrary, the possession of the Ph.D. (and this is the fourth point referred to) implies the possession of the technic of the branch of knowledge for which the degree was conferred. This is quite apparent if we take such a science as chemistry, where acquaintance with the methods is indispensable. A man must know how to use the methods; else he is not a chemist. But there is just as truly a technic of history, a technic of mathematics, a technic of archeology.

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* Read before the Association of American Teachers of Diseases of Children, May, 1920. Reprinted from Trans. Assn. Amer. Teachers of Dis. of Children, 1920.

Fifth, the Ph.D. implies that the possessor has done at least one piece of creditable research, his doctorial thesis. This again implies that he is familiar with some of the original literature, knows how to work in a library, and has developed some critical judgment.

Sixth, the Ph.D. placed after the name of one of your faculty implies that some university through its responsible experts has certified to all of the foregoing. Naturally these experts have found it necessary to subject the candidate to some sort of examination before such certification. Thorough written and oral examinations before faculty commitees constitute the ordinary mechanism for the purpose.

Naturally, your university in selecting a professor or instructor cannot look upon the degree alone as sufficient qualification for appointment; but at least the degree is a mark of serious preparation in some given speciality. And the Graduate School which conferred the degree is an organization for the education of specialists. The Minnesota idea, or experiment, is merely that the mechanism of the Graduate School can be used to instruct, standardize, and certify medical specialists exactly as well as scientific and literary specialists. It can give them thorough knowledge; it can give them technical experience; it can start them on the road to research.

Some of you may be inclined to think that the only diagnosis a doctor of philosophy in a teaching position is able to make is a diagnosis of ignorance; and that his only prescription is a dose of mathematics or chemistry or Latin—as the case may be. That his only death certificates are flunk notices; and that, finally, he is engaged in a despicable form of contract practice for a starvation salary. However, most of you on a little more reflection will admit that in the crisis of war the university scholar was able to extend expert service to the nation; that in the present condition of society his diagnosis and suggestions should be sought; and that the present drain of college professors into business and industry indicates that their specialized training and knowledge are valuable in the world of affairs.

The truth is that what the world needs is productive scholarship as exemplified by men who can grapple new situations, men with a broader training than that obtained in the ordinary college or in the experience of any business, manufacturing enterprise, or industrial process. The graduate school selects, trains, and certifies such scholars. No institution of learning is really a university unless it supports an active graduate school, where research and the training of investigators are the primary aims.

If we turn now to agriculture, which as a profession is based, like medicine, on applied science, we find that quite generally the certification of experts has taken the same form as that described for the expert in language, literature, or science. Doctor's and Master's degrees are given in University Graduate Schools in such subjects as soil chemistry, animal husbandry, and plant pathology. The holders of such degrees occupy, in large measure, the prominent positions in college work, government experiment stations, and private highly organized agricultural enterprises. In a considerable number of cases they establish offices for themselves and offer their services to the public on a fee basis exactly as do doctors of medicine. I know a man who is a doctor of curative and preventive medicine for timber. Lumber men "consult" him with reference to tree diseases and railroads call him to "cure" their ties and bridge beams. He tells them what medicine to use in particular situations, and they actually speak of this as timber "treatment."

In engineering, specialization begins in the undergraduate course. A man graduates as a civil, mechanical, electrical, mining, or chemical engineer. This is safe and practical in engineering, because the young engineer is not likely to assume any heavy responsibility. On the contrary, the young doctor's first case may be a life or death affair.

Quite in harmony with what we should expect, there is little real graduate work in engineering and little research in engineering schools. The same thing is true of law, in which self-made specialism is also the rule. It seems to me, therefore, that we in medicine should take our cue for graduate work from the sciences and agriculture, rather than from engineering and law.

I shall now try to make clear exactly how the University of Minnesota has adjusted the ideals and machinery of the Graduate School to train medical specialists.

The Graduate School is the division of the University which offers instruction in advance of the bachelor degree. It is consequently the division chiefly concerned with research and with the training of investigators and specialists of all kinds. The Dean of the Graduate School is Professor Guy Stanton Ford, head of the Department of History. The school has an executive commitee with members representing subjects such as social science, natural science, medicine, and agriculture. It has a faculty consisting of those men in any department of the University who have been chosen by the Dean and Executive Committee as fitted to give advanced instruction and train research students. The Mayo Foundation for Medical Education and Research is a part of the Graduate School, and certain of its members are on the Graduate School Faculty. Similarly, certain members of the Faculty of the Medical School are members of the Graduate Faculty.

All graduate work is conducted under general rules prescribed by the Graduate Faculty, but the detailed control of each great branch is under a special committee; for example, the committee for Agriculture and the committee for Medicine. The latter committee consists of the President of the University, the Deans of the Graduate and Medical Schools, Director Louis B. Wilson of the Mayo Foundation, Professors J. P. Sedgwick, C. M. Jackson, J. C. Litzenberg and L. G. Rowntree of the Medical School, and D. C. Balfour, W. F. Braasch, and M. S. Henderson of the Mayo Foundation. The committee, which is organized as two sub-committees located respectively at Minneapolis and Rochester, is the immediate administrative body for all graduate work in medicine and makes recommendations to the Dean and Executive Committee of the Graduate School (and through them to the Board of Regents), on the appointment of fellows, the appointment of members of the Graduate Faculty, the conferring of degrees, etc. Particularly this committee is charged with recommending the annual budget of the Mayo Foundation.

Under this organization a student may work for the degree "Master of Science" or the degree "Doctor of Philosophy" in any of the preclinical sciences, such as anatomy or pathology, or in any of the clinical branches. For admission to graduate work in the sciences a bachelor's degree is required; for work in the clinical branches the M. D. degree from a Class A school and a year of internship are required, in addition to the bachelor's degree or its equivalent.

Many of the graduate medical students—but not all—hold fellowships. By this is meant they receive small annual salaries and are expected to give a certain amount of service. At Minneapolis the fellows assist in the clinics, or in teaching medical students, or in the conduct of the University Health Service. The Burch Fellow assists at Dr. Burch's office. There is a new fellowship in tuberculosis supported by the Hennepin County Anti-Tuberculosis Committee. We hope to see a large number of such fellowships gradually developed as endowments or temporary gifts.

Educationally the service, whether teaching or assisting, is valuable, because it contributes to the student's knowledge and power. Economically the system of fellowships finds endorsement in the fact that few men are able financially to undertake a long graduate course after the six years of the regular medical course and the year of unpaid internship. It is not essential to the plan, however, that all graduate students hold fellowships. Some pay their own way and carry on their studies without obligation of service.

All graduate teaching is essentially individual. There are few classes; few required lecturers. Every student is under a faculty advisor who is responsible for making out the student's program from year to year. Every student selects his major subject and also a minor or supporting subject. For example, major in pathology and minor in anatomy; or major in pediatrics and minor in biochemistry. The student's advisor must see that the student gets thorough, all-round training in his major, a fair knowledge of his minor, and also sufficient knowledge of any other work which may be fundamental to either major or minor. At the beginning of the second year's work each candidate for the Ph.D. is required to submit, with the approval of his advisor, a tentative program for his entire course, which requires the approval of the Graduate Medical Committee.

The primary purpose of the graduate school is to make productive scholars. Productive scholars must be able to earn a living; consequently they must be trained as skilled specialists in practical technical fields. Really these are two aspects of the same job which the graduate school must do. The training of scholars takes time; hence the rule requiring at least two or three years for an advanced clinical degree. A scholar must be familiar with the literature of his specialty, hence the requirement of a reading knowledge of French and German. The test of productive scholarship is original investigation; hence a thesis involving new facts in some phase of the major subject is required. The certification of advanced scholarship is a serious responsibility; hence the graduate school demands searching written and oral examinations of all candidates for the Ph.D. degree. For the Master's degree in the clinical branches as thorough training is expected in diagnosis and other technical procedures as for the Ph.D. degree. But the thesis and the final examinations are not so exacting.

These in general are the requirements. They are quite different from those of an undergraduate school. There is no hand feeding, no formal reciting, no prescribed lessons, no reporting of absences, no routine laboratory exercises. The essential environment consists of libraries, laboratories and clinical material, with competent supervision—and, above all, criticism. The student with his advisor as a guide is turned loose to educate himself. Mostly he learns by doing, which is the natural way. If he has stuff in him, he arrives. If he is only an imitator or absorber or bluffer, he shows what he is.

In the winter quarter the University of Minnesota had 169 graduate students in medicine who were candidates for higher degrees, 37 of whom were at Minneapolis and 132 at Rochester. There were also 23 graduate students at Rochester and a few at Minneapolis who were not candidates for advanced degrees. This is the largest number of strictly graduate medical students anywhere. About 20 will come up for degrees at the coming commencement. The student body is of a very high order. There are many more applicants than available places, particularly in surgery, urology, pediatrics, and otolaryngology.

Now, if you have followed this hasty sketch you will see that in a sense every medical school and every good hospital is a center of graduate work. There are assistants in the laboratories and clinics who render service and receive in many cases small salaries, but who are there primarily to learn. However, you who are teachers do not usually think of these men as students. You assume no responsibility for their education. You do not lay out definite work for them; especially you do not look to their training in the fundamental sciences. You may favor research, but few feel it their duty to insist upon it as part of the training of assistants. Your institution takes no responsibility for these men; does not acknowledge them, when they leave you, as alumni. Many of them go out well trained, but you have no standards which they may set before themselves and which you may enforce. There is no goal to be striven for. There is no certification of quality which either the man can value or the public can rely upon. It is just in these particulars that we believe the Minnesota plan of supervised, formal education to be superior to the hit or miss method under which most specialists in this country—practically all, indeed, worthy of the name—gained their right to that title of distinction.

To accomplish our purpose we have to arrange matters that would not be thought of unless we had in mind the ends to be attained. We know that good training in the laboratory branches is essential and that the undergraduate medical student gets only the elements of these subjects. We have to arrange that the graduate students shall have time for such work; that materials and a place to work are provided; that instructors are at hand when needed. At all times about 25 graduate students, many of whom are majoring in clinical branches, are at work in the Department of Anatomy. More are in pathology; some are in biochemistry. The Department of Physiology gives advanced work in optics for students of Ophthalmology, and so on. This adds work, but also interest and enthusiasm to our laboratory departments.

Then there is the thesis, required for reasons already set forth and highly valued in our scheme of education. A student cannot do research if he is kept busy all day examining patients. We have to arrange time for research. At the Mayo Foundation the fellows are on a "double session." One group works in the clinic mornings and the other afternoons. Every man has several hours each day for work in the laboratories and for seminars, demonstrations, reading, experimentation, etc. At Minneapolis our system is less formal, but we see to it that ample time is provided for these purposes. You must do this if you wish to produce a scholar rather than a technician.

Our ideal that these men are students and not employees or assistants or servants is kept always before us in considering their welfare. One of the fellows in Pediatrics is now in New York for some special study. His stipend goes on. Dr. Jackson tells me he recently found one of the Mayo fellows in the Surgeon General's library digging away on his thesis bibliography. His expenses were being paid by the Mayo Foundation.

In clinical training, also, supervision is exercised. In surgery care is taken that operative skill is not put before diagnostic ability. In medicine the comparative study of complete histories of cases in large groups and the laboratory side are insisted upon. In pediatrics experience in contagious diseases is required. Just now one of the fellows in pediatrics is serving as resident in contagious diseases at the Minneapolis General Hospital, and the University continues his stipend. Another fellow is to go there as resident in Medicine.

In our opinion it is the graduate school with its definite requirements and rigid rules which influences students and faculty alike toward concrete ends, well thought out in advance. One has but to note the responsibility which the professor feels for his graduate students and the pride he exhibits over their achievements, in order to be convinced of the advantages of our plan of organization. Once a quarter at Rochester each student is graded by his advisor on the basis of personal knowledge. This tends to a feeling of responsibility on the helpful part of instructor and creates a constantly critical as well as helpful attitude.

The University of Minnesota began the plan of graduate medical teaching six years ago. The Mayo Foundation became part of the university five years ago. The first degrees were conferred three years ago. The war interfered with our work, but the following list gives the names and thesis subjects of the men graduated in clinical branches during the past three years:

G. L. McWhorter, Ph.D. (*Surgery*): "Some Clinical and Experimental Observations on Gastric Acidity."

Rood Taylor, Ph.D. (*Pediatrics*): "Hunger in Infants."

H. W. Woltmann, Ph.D. (*Neurology*): "The Brain Changes Associated with Pernicious Anemia."

R. E. Morris, Ph.D. (*Medicine*): "The Graphic Recording of Reflexes, Clonus and Tremors."

E. L. Crispin, M. S. (*Medicine*): "Clinical Studies in Abdominal Disorders."

F. B. McMahon, M.D. (*Surgery*): "Primary Pulmonary Carcinoma and Its Roentgen Diagnosis,"

H. W. Meyerding, M. S. (*Orthopedic Surgery*): "Cystic and Fibrocystic Disease of the Long Bones."

A. W. Adson, M.S. (*Surgery*): "Experimental and Clinical Results of Nerve Anastomoses."

V. C. Hunt, M.S. (*Surgery*): "Torsion of Appendices Epiploicæ."

F. A. Olson, M.S. (*Surgery*): "A Study of the Roentgenographic Findings in Renal Tuberculosis."

J. De J. Pemberton, M.S. (*Surgery*): "Blood Transfusion."

C. E. Nixon, M.S. (*Neurology*): "The Pathogenesis of the Lesions of the Nervous System Found in Cases of Pernicious Anemia."

Carleton Dederer, M.S. (*Surgery*): "Transplantation of the Kidney and Ovary."

E. J. Horgan, M.S. (*Surgery*): "The Histogenesis of Carcinoma in the Islets of the Pancreas."

I. W. McDowell, M.S. (*Surgery*): "Cancer of the Stomach."

W. O. Ott, M. S. (*Surgery*): "Surgical Aneurysms."

W. J. Tucker, M.S. (*Surgery*): "Infections of the Kidney."

T. B. Reeves, M.S. (*Surgery*): "A Study of the Arteries Supplying the Stomach and Duodenum and their Relation to Ulcer."

E. H. Weld, M.S. (*Surgery*): "Renal Absorption with Particular Reference to Pyelographic Mediums."

J. L. Butsch, Ph.D. (*Surgery*): "Ulcers of the Gastro-intestinal Tract with Special Reference to Gastrojejunal Ulcers."

L. W. Barry. Ph.D. (*Obstetrics and Gynecology*): "The Effects of Inanition in the Pregnant Albino Rat with Special Reference to the Changes in the Relative Weights of the Various Parts, Systems and Organs of the Offspring."

"Not a very formidable list," you may say. But they are all good men. Five of them are now on our medical faculty. One is on the faculty of Rush Medical College. Several are on the staff of the Mayo Clinic. When other universities begin to call men of this type of training to their chairs, we shall have medical faculties which are more than selected representatives of the local practitioners. Our medical faculties, like our arts and science faculties, will be cosmopolitan bodies of productive scholars.

Perhaps we may even solve the perplexing problem of the full-time teacher in the clinical branches by creating a race of doctors interested in the pursuit of science and in the academic life! This may be a vain dream, but during our long polar winters in Minnesota it is pleasant to dream.

However, we naturally expect that most of our graduates will go into special practice. We think they are prepared. They may not, at graduation, have had as much clinical experience as those who spend an equal time as assistants in a big clinic. But we believe that the better foundation in science and theory, the stimulus of systematic study, and the experience in research more than counterbalance. We know that the practitioner will be in contact with cases all his life; with teaching laboratories, perhaps never again.

Now the reaction of some of you to what I am saying may be something like this: "This is a fine scheme. But it must take a lot of money. A rich university like Minnesota can carry it out, but we could not." That's just where you make a mistake.

The University of Minnesota is not rich. It is true that we have the splendid facilities of the Mayo Foundation. But without that and without more money than the Medical School needs for undergraduate teaching, we could do something worth while.

Every major university has a graduate school. Probably your laboratory departments of the medical school are already part of it. You have but to organize your clinical departments in relation to the graduate school, lay out your courses of study, enroll your instructors, residents and other existing clinical assistants as students, and think of them and treat them primarily as students. As soon as you create this atmosphere for faculty and students alike, you will have a graduate school of medicine on the Minnesota model. On account of the informal nature of the instruction and the use of existing facilities, the expense will be slightly, if any, greater. We believe it will pay you to consider this subject.

Naturally the question arises whether the universities of the country could supply the need for specialists if all were to be trained as I have outlined. Can we expect that at some time an advanced degree will be the universal title to specialism?

The Committee on Graduate Work of the Council on Medical Education has recently reported, through its chairman, Dr. Louis B. Wilson, that there are above 2,000 assistantships, residencies, etc., in the Class A medical schools. This would be a considerable body of students if organized and instructed as our plan demands. It is from this body that specialists have been and are chiefly recruited. But is this number adequate?

Dr. Wilson's figures show 235 such places in Ophthalmology and Otolaryngology. However, Dr. Edward Jackson, of Denver, has estimated that this country needs 10,000 ophthalmologists—one to 10,000 population—and that 400 new ones will be required each year. I think it will be agreed that the existing clinical facilities of medical schools would not properly train such a number. But does that mean that the universities should not attempt to meet the need nor contribute the great weight of their influence as examining and standardizing institutions? I think not.

In the first place the universities constitute the only place where training in the science laboratories can be obtained. They must hold out the necessity of such training for specialists and prepare themselves to give it. The medical teachers, both laboratory and clinical, must stand ready to supervise research, approve theses, and offer final examinations. As for clinical training, it matters little where it is obtained, provided it is good; and the graduate school is broad-minded in the matter of *in absentia* study. I offer the suggestion that, gradually, strong clinics all over the country may become affiliated with graduate schools, and their assistantships take the form of fellowships under the Minnesota plan. The university, of course, must assume the responsibility for the adequacy of the instruction and for the final certification of the student. But I believe this is a legitimate function of a university which less and less will be a cloister, and more and more a part of the world. Such a plan, universally carried out, would at length make the universities the training camps for medical specialism just as they are now for pure science.

We are, perhaps, about to take a significant step in this direction at Minnesota. The Chief of our Department of Ophthalmology and Otoalryngology, Dr. Wm. R. Murray, has outlined a one year course in laboratory and theoretical work for prospective specialists in his field. Very little clinical work would be included, the students being expected to get that later in special clinics or hospitals for eye, ear, nose and throat. No degree or certificate would be given for the one year course; but one has but to imagine a student, after this year, securing the privilege of "on leave" registration in an approved clinic, selecting a topic for research and carrying it to completion in a satisfactory manner, and finally passing satisfactory examinations in accordance with the rules of the graduate school, in order to obtain a degree from the University of Minnesota. It is not at all impossible that this may happen in particular instances. Personally, I hope it will happen.

You will note that I have said nothing of short courses, nor of the so-called post-graduate schools existing apart from universities. The Committee of the Council of Medical Education, already referred to, has recently visited all such schools, and you are referred to the excellent report about to be published. Suffice it that these schools chiefly supply continuation courses for general practitioners and extension courses for men already partially trained in a clinical specialty. "Few (post-graduate) schools attempt to give complete special preparation for practice in limited clinical fields."

That there is need of opportunities for practitioners to obtain additional training in short courses there can be no doubt. But I cannot see how medical schools with undergraduate classes can supply this need. What is required for the practitioner on vacation is well organized class instruction for small groups, with ample clinical material for illustrative purposes. The undergraduate medical school can fit long-term graduate students into its organization as assistants and teaching fellows to the actual strengthening of iundergraduate teaching. But it cannot admit groups of short time students in any such way. The medical school may admit physicians to regular classes and clinics and to its laboratories. It may organize summer courses. But it can hardly be expected to do more.

My notion is, therefore, that short courses for practitioners should be developed in special schools organized for the purpose. I do not like the name "post-graduate," and perhaps a better one can be found. In the great cities there are hospital facilities not used for undergraduate medical instruction. They ought to be used for courses for practitioners. The important question is organization and staff. As long as only fees are available, the best results are far away.

I should like to be turned loose in New York with a free hand and five million dollars of endowment. I would organize short courses for practitioners with competent paid instructors. I would tie up the school with the Extension Department of some university, for there is where short course instruction belongs. But I would have all my full-time assistants enroll in the Graduate School under the Minnesota plan. With this two-edged sword I should expect to make some havoc with hydra-headed ignorance. But this again is a cold-storage dream. which we will now carefully place next to the ammonia coils in the archives of this society. Perhaps fifty years from now some one may bring it out and say "what a good suggestion that is, and in such a good state of preservation!"

Having wound up and run down, it only remains to stop. I shall be satisfied if I can strike twelve before the pendulum ceases to swing.

1. Specialism is a necessary and permanent part of medicine.
2. The education of specialists is very important.

3. All prospective specialists need further training in the laboratory sciences.

4. All prospective specialists should learn the history and literature of their field.

5. All prospective specialists should learn research methods.

6. As many specialists as possible should be competent and continuous contributors to the specialty.

7. Every specialist should be a competent clinician.

8. The university is the best organization for giving these various sorts of training.

9. The university should standardize, supervise, and certify with appropriate degrees, this training.

10. The graduate school was organized for just this purpose, so far as science and language are concerned.

11. The training of medical specialists under the graduate school organization and ideals is the Minnesota plan.

12. The Minnesota plan works.

13. (This clock is a little out of order!) The organization of short courses for practitioners, though important, cannot be done adequately by the medical school or the graduate school, but could well be developed in metropolitan centers under university auspices in connection with the extension department.

THE ORGANIZATION OF MEDICAL SCHOOLS AND HOSPITAL FACILITIES FOR GRADUATE MEDICAL EDUCATION*

E. P. LYON

I shall discuss three topics, the first two of which pertain to graduate medical education directly. The last concerns our state university medical school, and therefore concerns graduate work indirectly.

It is evident that two types of post-degree work need to be carried on. The first of these is the type of education needed to make medical specialists in the real sense of that term. Such a course, as you all know, does not consist of three weeks or three months. It is a matter of years; nobody knows how many; but surely three or more years under good auspices must be put in by the medical graduate before he can be a competent surgeon or a competent internist.

The University of Minnesota has instituted a plan of instruction for medical specialists under the same organization and ideals as those which are used in the universities all over the world for the production of specialists in other fields of human endeavor. The chemist, the historian, the expert in agriculture, and so on, are all graduated under the system which I shall describe. Our idea is that medical specialists can be taught in the same way; and what we call the Minnesota plan is merely the application of the ideals of the graduate school to medical education.

There are four or five points which are common to this type of education everywhere. There is first the machinery or organization under which it is accomplished. The graduate school is not a school of buildings and classes in the ordinary sense, as people are accustomed to think of a school. It is rather a faculty of teachers; and its organization is superposed, as we might say, on the other schools and colleges. Just as you belong to the county society, to this society, and to the state society, so there are in the university men belonging to various faculties. From these groups of university men in all the fields of learning, those who are best qualified to teach advanced work are picked out and belong also to the graduate faculty. The graduate school is, therefore, not a school of buildings or laboratories, but is rather a faculty and a group of advanced students. I am not dean of that faculty; the professor of history happens to be.

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* Reprinted from Minnesota Medicine, 1921, iv, 90–95.

Second, graduate education in all branches is informal. Of course, you all know real education is individual, and that a man educates himself. You are here in this meeting really for the purpose of continuing your education. So it is in the graduate school—each man educates himself with the help of those who are expert in the line he wishes to pursue. Each man has an advisor under whom he works and who lays out a program for him. That is the way we do, both at Minneapolis and Rochester.

In the third place, a man having decided on his main branch must prepare himself, also, along allied lines or else he is not a true specialist. He must know those facts and methods which are the foundation of his work. We have him choose his "major" and "minor" subjects. Then we have a program laid out which involves the necessary foundation sciences for his specialty.

If he is going into internal medicine, he goes back to physiology; back to chemistry. If it is surgery, he takes up anatomy, pathology, and so forth. You all know when you come to think of it that in the ordinary four year medical course you got only the elements of these laboratory branches. Therefore our plan involves a more thorough knowledge of particular sciences that one needs.

It is of course essential that a man have also a thorough clinical knowledge of his specialty. We try to see to it that the specialist is well trained clinically. We feel, however, that a person going into any given specialty is bound to be with that all of his lifetime, whereas only for a limited time will he have access to good laboratory facilities.

We feel, fourth, that a man must be acquainted with the literature of his specialty, and hence we have requirements of language tests. We feel that a specialist should be a contributor to his specialty and should know the methods of research. Therefore the requirement of a thesis. And finally there are comprehensive examinations that will test a man and show that he is qualified for an advanced degree which is merely the sign of qualification of a specialist, from the university as a standardizing agency.

This, in brief, is exactly the way historian is produced; that a chemist is produced; and that an expert in soils is produced. This is the Minnesota plan of graduate medical education which is in vogue in connection with our hospitals at Minneapolis, with our laboratories, and with the Mayo Foundation. The latter, you understand, is not a part of the medical school, but is a part of the graduate school of the university.

It is a source of great pride to us (and I think many of the practitioners of the state share with us in this feeling) that we have the largest strictly graduate school of medicine in the world. We have about 200 students in the two places.

You will note, if you stop to think of it, that our plan is really nothing new. It is what has been done before, with one exception. The exception is very important, and I shall try to make it clear.

Dr. Wilson as chairman of a committee on graduate medical instruction, appointed by the Council on Medical Education of the American Medical Association, investigated how men become surgeons, urologists, eye and ear men, and so forth. He found, taking the good ones, that the chief method that has been used in the past and that is in use now is that they should serve as "assistants" in a good clinic for two, three, or more years. The doctor calls his helpers "assistants"; but from the young men's standpoint, they serve their assistantship for the purpose of becoming efficient in the specialty. Now our idea is that those young men be regarded as students and not as hired men. If you go to the Mayo Clinic or the University Hospital you will see young men working there. They will look to you like assistants, and they are assistants; but we take a different point of view regarding them. We say they are not the servants of the clinic, but primarily students. We call them "fellows." As soon as you make that slight transition in regard to your assistant, you have made a great difference in your attitude toward him and in his attitude toward his work. You lay out a man's program not with reference, primarily, to how he can best help you, nor how he can best contribute to the efficiency of the hospital or clinic, but how you can best help him. As an outsider (because I am a physiologist and not engaged in clinical medicine) I have been surprised to see the difference in the attitude of our men, both at Rochester and at Minneapolis, as soon as they began to regard the young doctors as students primarily and ceased to regard them as assistants primarily. You would hesitate to send an assistant perhaps to the anatomical or pathological laboratory for three or six months and pay his salary;

but we do not have any hesitancy in sending these men, if that is what they need.

As I have tried to analyze the situation in my mind, I have become more and more persuaded that the essential point in the Minnesota plan is the taking of the assistantship and making it a graduate studentship, and considering the obligations of the institution toward these men along that line. You can see how this may affect the organization of hospitals and may be extended to hospitals not immediately connected with medical schools.

I hope I have conveyed to you clearly what our main idea is in the graduate medical school of the University of Minnesota. As I have said, it is exactly the same idea applied in regard to medicine that for years has been applied successfully to the natural sciences and social sciences, and to languages and literature. That is the first topic I had in view.

A second thing I want to speak of is the type of education, which is apparently needed by ordinary practitioners in the form of review courses or short advanced courses by which in the short time which they can spare from practice they can gain information and make themselves more proficient along some line or master some new technic. That is what so-called post-graduate schools attempt to do. Dr. Wilson if he were here could give you definite information on this subject, as he has visited these schools all over the country. But that, in the main, is what they attempt to do. None of them, I believe, has mapped out anything like a complete course to fit men for a specialty, although they may give a part of it.

This second type of education is a difficult thing to organize, and I do not think it has been done satisfactorily in this country. If you attempt to do it in a medical school of the undergraduate type you meet with great difficulty. At Minneapolis, for example, we have a faculty and certain clinical facilities; and both are occupied in taking care of a large body of undergraduate students in a definitely laid out year course. To separate certain parts of this instruction and organize short intensive courses, such as are needed by practitioners who can only spend three or four weeks in study, would upset the whole curriculum. We have not been able to do it. Our faculty is too small and our facilities are too limited. Although I recognize the need, I do not see how it can be met—I mean adequately, from an educational standpoint.

In my opinion, what is needed for practitioners is a large, independent endowment and a special faculty in connection with ample facilities in large hospitals which are not used for undergraduate instruction.

If you want to get a definite course in clinical pathology or cystoscopy or some other branch four or six weeks, somebody must be paid to give it. The fees you can pay are insufficient; just as the tuition you paid as undergraduates was insufficient to supply good instructors. State aid or endowment was needed.

You do not wish, moreover, to sit on a bench and hear lectures. You want to do the actual work under strict supervision. Certain men will have to give a large amount of their time to this form of teaching, and it does not appear that the thing will be done right until we have special organizations for it in connection with clinical facilities not used for undergraduate teaching in the large cities.

While, therefore, we cannot organize postgraduate work at Minnesota, as some of you knew it in Berlin and Vienna, we will do all we can for you; and perhaps there is more up at Minneapolis than you know. All of our lectures, clinics, dispensary work, laboratory courses, and so on are freely open to any practitioner who wants to come there for a few days or weeks as a visitor. If he wants to stay a longer time he can do so as a special student. There are special laboratories of animal surgery and experimental medicine, and we have full time men in charge of them. The same is true of the anatomical, bacteriological, pathological, and physiological laboratories. They are well equipped, and we have good men in charge. You will find they will give you any assistance in their power.

The "Physicians' Days" of special clinics which were discontinued on account of the war may not be resumed, because the Minneapolis members of our faculty will coöperate in the "Clinic Week" of Hennepin County, which places all the clinical facilities of Minneapolis at the disposal of visiting doctors. Our university clinicians in St. Paul likewise will take part in the "Clinic Week" of that city. However, I want you to know we have your needs in mind; and as far as we can, consistently with our obligation to our undergraduate body, we will use our facilities and our institutional forces to meet the needs of the medical profession.

You have here today a body of influential medical men of the state; and I want, third, to say a word to you about the medical school of the state university. I venture to say that you all believe that the medical school ought to be ample for the needs of the state as an undergraduate institution; and I presume most of you take the position that it should be ample for the needs of the state as a graduate institution as well. Most of you would go a step farther, on account of its strategic situation geographically (with no school between Minneapolis and the western coast) and say that our school ought to be ample for the needs of the great northwest. The question is, can it meet these needs?

It is a good school. We have no need to be ashamed of it. I am going to give you some information which I got in a roundabout way from the dean of another school. He wrote letters to about twenty-five of the leading medical educators, asking them to give their opinion as to the twelve leading schools of the country. The last time I saw him he had received 18 resplies, and Minnesota was on every list except one. Therefore you see a large number of men who are posted on medical education believe we have a good school in this state.

But that ought not to make us self-satisfied and complaisant. We all see there are ways in which the school can be improved. Every department should be strengthened, but the place where we are the weakest is on the hospital side. Ever since I have been here, now seven years, we have been working and working, and not a single thing has been added to the hospital in that time except a service building, which was constructed soon after I came. We need 500 or 600 beds instead of 200. I think you will all agree with that proposition abstractly. It is in regard to how to get them and how to run them that questions arise.

We have a great many problems; but I will touch on only one of them, that of clinical personnel. If we wanted an anatomist tomorrow, everybody here would say, go and get the best man that can be found anywhere in the world and have him give his whole efforts to teaching that subject. You would not wish to have him practice medicine one-half or three-quarters or ninety per cent of the time. You would say, pay him sufficient salary so that he may devote his whole time to anatomy. It is the same with regard to pathology, pharmacology, physiology, and bacteriology.

When we come to the clinical departments we meet with great difficulty and difference of opinion; that is, how to select men, what type to get, what arrangements can be made with them. I do not know where we are going to arrive; but I am frank to say to you that this problem is the hardest one in medical education to solve, and I bespeak your thoughtful, careful, friendly consideration of it.

Shall the teacher of surgery, medicine, or obstetrics devote his whole time to research and teaching, and not practice at all? Some people advocate this. There are two reasons why our university cannot do it. First, we have not adequate hospital facilities to attract such men, and the second is, we cannot command salaries large enough.

But I for one do not believe in that plan. I think our clinical teachers ought to have an intimate relation with medical practice in some form or other. But how?

In the old days medical colleges picked out a local practitioner who was best known in his line, who had the best reputation or biggest practice and made him professor of medicine, or professor of surgery. But it was found there were distinct limitations in educational efficiency connected with this method.

When a man even with the best intentions devotes part of his time to teaching and the other part to practising medicine, there must be occasions in which he must put the work of attending to his patients first, because he has assumed a vital responsibility toward them. Moreover, the natural tendency always is to take more practice as it comes, and this seriously hampers a teacher's work in connection with the university. Some men, furthermore, are not entirely conscientious in regard to their school obligations. Finally the busy practitioner is seldom an investigator of authority; nor as a rule can a man who has gained fame in medical research retain his standing in that regard if he begins on an active outside practice.

In spite of all these drawbacks, I advocate some kind of arrangement by which the clinical professor may maintain relationship with the medical profession—an arrangement which shall make him really part of the profession.

It must be an arrangement which makes the educational side truly vocational, and which makes practice merely secondary or avocational rather than the man's primary work. For instance, the chief of the department of medicine ought to be primarily a teacher and investigator. His relation to the outside ought to be secondary.

Let me repeat, medical education in the clinical departments is between the devil and the deep sea. On the one side is the part-time instructor who is primarily a practitioner and only secondarily a teacher. On the other side is the cloistered scientist with no knowledge of practice and no common bond with the medical profession. We should, *we must, indeed,* avoid both these extremes.

The plan which I believe is the best is what I have called the geographical full-time plan. A man in medicine or in surgery or in any of the main clinical departments in a university should do all of his work *in one place* and under one organization and one administration. That again may strike some of you as being impossible of accomplishment because it involves so many things which you think a state school should not do. I hope to show you that such is not the case.

If our teachers do all of their work in one place, it means the university hospital has got to have three classes of patients: first, those who do not pay at all; second, patients who pay for their bed and board, the so-called per diem patients; and third, we must have those who pay for their professional care also.

You are all doubtless willing that the medical school should care for the pauper sick of the state. You would like to see the university charity hospital enlarged, but there we strike the legislature. They are not willing to go any further in the matter of a free hospital. Moreover, the Board of Regents are not willing to use university funds to any greater extent for the support of free beds.

Many of you would probably be willing that we take the second class or per diem patients. You hesitate in regard to pay patients. That is where our conference with a group of Twin City doctors came to the point of opposition. They were perfectly willing that the university hospital should have free patients; and every one, except perhaps one or two, said he was willing that the university should take a class of patients paying for their bed and board. They were willing finally that our professors should have a hospital across the street for private patients, but they were not willing to have pay patients on the campus of the university.

We ought to work out this problem together; and I want to point out, from my standpoint as a physiologist, that I should very much dislike to have one laboratory on the campus, another across the street, and another perhaps over town. With such an arrangement I could not do my work satisfactorily. Geographical unity is very essential to my department of physiology, and I believe it is equally essential to the department of medicine or to the department of surgery.

There are excellent reasons from the educational side why we should have all types of patients. From the financial side it is indispensable, as in no other way can we support the best type of clinical teachers. In no other way can we make them university men in the fullest sense and at the same time active members of the medical profession.

We will best conserve the medical school and best conserve you as a profession if you can bring yourselves to the point where you are willing to assent to the principle of geographical full time and not be upset by its minor implications.

Under this plan all patients would be under the university roof and under one organization. All fees and charges would go to the hospital. There would be better opportunity and facilities for interns and nurses and graduate students and for the active profession. It is the plan in use in Michigan and just adopted in Wisconsin, and nearly like that used in Iowa.

Competition under this plan would surely be less than if the clinical teachers with university prestige have offices in town and the right to consult all over the state. The only argument you have to fall back on is that of public policy. Are you ready to say that the university should have no relation to the practical affairs of life? That it should go back to the cloistered seclusion of the middle ages? I cannot believe that the intelligent medical profession of Minnesota is willing to take such a position.

I believe that the geographical full-time plan is the solution of the university medical problem. I bespeak your careful study of it, and trust and believe that you will give your assent to it when the time shall come.

GRADUATE INSTRUCTION IN ANATOMY*

CLARENCE M. JACKSON

The graduate work in anatomy involves two distinct problems: (1) the question of the training of professional anatomists; and (2) the graduate work in anatomy for clinicians. These will therefore be considered separately.

THE TRAINING OF ANATOMISTS

The graduate work desirable for the training of a professional anatomist will depend largely upon the amount and character of his previous study. It is therefore necessary to consider the matter from the beginning of the college work. Let us imagine that at this point a young man has already decided on a future career in anatomy and that he asks for advice in planning his future work. We should point out the various possible paths leading in this direction, and explain that the best plan will vary somewhat according to individual circumstances. For convenience, we may divide the probable course of training into three stages, subject to a certain amount of overlapping and difference in sequence in individual cases. These stages include: (1) the fundamental academic or general college work; (2) the professional work, including elementary courses in anatomy and allied subjects; and (3) the graduate or advanced anatomical work. The essential subject matter for each stage will first be outlined, leaving the question of degrees for later consideration.

Academic or general college work. The present committee is unanimous in considering as an indispensable at least two years of general college work, including the fundamental training in physics, chemistry, and biology (zoölogy), as generally outlined for premedical courses. It is highly desirable (considered essential by Evans, Stockard, Streeter, and Terry) for the future anatomist to extend his general college work to three or four years, which will enable him to obtain much without which he would find himself more or less handicapped in his later career. The additional time would permit a more thorough grounding in the sciences, especially biology, which should include comparative anatomy (Huber, McMurrich, Terry, Jackson) and, incidentally, microscopic technic (Evans, Terry). Dr. Bardeen emphasizes the value of training in physical anthropology. Other desirable subjects mentioned are mathematics (to calculus) and psychology. Of the foreign languages, a reading knowledge of French and German is essentail; Latin and Greek also are desirable. Dr. Terry urges the importance of other cultural subjects, such as history, art, and philosophy, and a thorough training in English.

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* Report by the Chairman of the Committee on Graduate Instruction in Anatomy, read at the Annual Congress on Medical Education and Licensure, Chicago, March 1, 1921. Published in the American Medical Association Bulletin, 1921, xv, 61–67.

Professional work in anatomy and allied subjects. For a Professional anatomist in a medical school, a thorough preparation in human gross anatomy, histology, and embryology (including neurology) is clearly essential. This would be covered by the courses required for medical students in the best schools. Further elective courses (e.g., topographic anatomy, history of anatomy, etc.) are desirable.

Of the allied subjects, physiology is generally considered the most valuable, on account of the close correlation between form and function in living organisms. Biochemistry is necessary in order to understand the fundamental conditions of morphogenesis. Pathology is also considered essential, since abnormal conditions often throw much light on the normal structure.

As to the necessity for the anatomist to have a knowledge of clinical medicine, there has recently been much discussion and difference of opinion. Considered from the theoretical point of view, it is true that a thorough scientific mastery of anatomy is quite possible without a knowledge of clinical medicine. But, on the other hand, it is very desirable that the teacher of anatomy in a medical school should have an adequate knowledge of how the subject is applied in clinical work. This will make his instruction more efficient, and give him a better insight into various phases of human anatomy. The present committee appears unanimous in considering it essential for the anatomist to have at least a reasonable degree of familiarity with clinical medicine, expressed by Dr. Stockard as an "acquaintance with clinical problems and the general application of anatomical knowledge in medicine and surgery." The majority of the committee believe that it is very desirable for the anatomist to complete the entire medical curriculum.

Graduate or advanced anatomical work. The committee agrees that in all cases the training of the anatomist should include substantial research work under competent guidance in anatomy or some closely related phase of biology. The demonstration of ability in productive scholarship is indispensable. The time required for this will naturally vary in individual cases. The minimum stated is "at least one year" (McMurrich); the maximum mentioned is five years (Huber). Most of the committee members consider two or three years necessary, the majority referring to a requirement equal to that for the Ph.D. as desirable. The possiblities of research work within the medical curriculum will be considered later.

Since teaching is usually an essential part of a career in anatomy, some experience in this line is clearly a desirable element of the training. Dr. Streeter suggests a year of teaching in one of the fundamental sciences immediately following the general college work. Dr. Bardeen recommends a year each in gross anatomy, histology, embryology, and and neurology. If limited in amount (averaging not more than one or two hours daily), so as not to interfere with research work, such teaching is unquestionably of great value in giving a more thorough mastery of the subject matter, as well as useful experience in pedagogic methods. Teaching fellowships should provide such an opportunity for capable advanced students.

The degree question and time requirements. All of us would agree that for the training of an anatomist the essential thing is the work previously outlined. This should be done in one of the better institutions, insuring proper facilities, guidance, and inspiration. With this proviso, the question of where the work was done (college, medical school, or graduate school) is of comparatively little importance, as are likewise the degrees obtained (B.S. or B.A., Ph.D. or M.D.). The essential point is to train an anatomist who is a productive scholar and a good teacher. The degrees themselves are of value only in so far as their requirements may outline a systematic and desirable plan of work, for which the degree is the goal and the certificate of achievement.

If we look over the work outlined here as desirable for the training of the anatomist, we find that the general college work will usually lead to the bachelor's degree (at once if four years are taken; one or two years later, if only three or two years of general college work are taken, followed by entrance into a medical school on a "combined course" in arts and medicine). We likewise find that the essential fundamental work in anatomy, together with the desirable allied laboratory and clinical subjects will correspond roughly to the requirements for the M.D. degree. And finally the necessary proficiency in research work corresponds approximately to the requirements for the Ph.D. degree. (The Master's degree, M.A. or M.S., may often be taken to advantage on the way toward the Ph.D.)

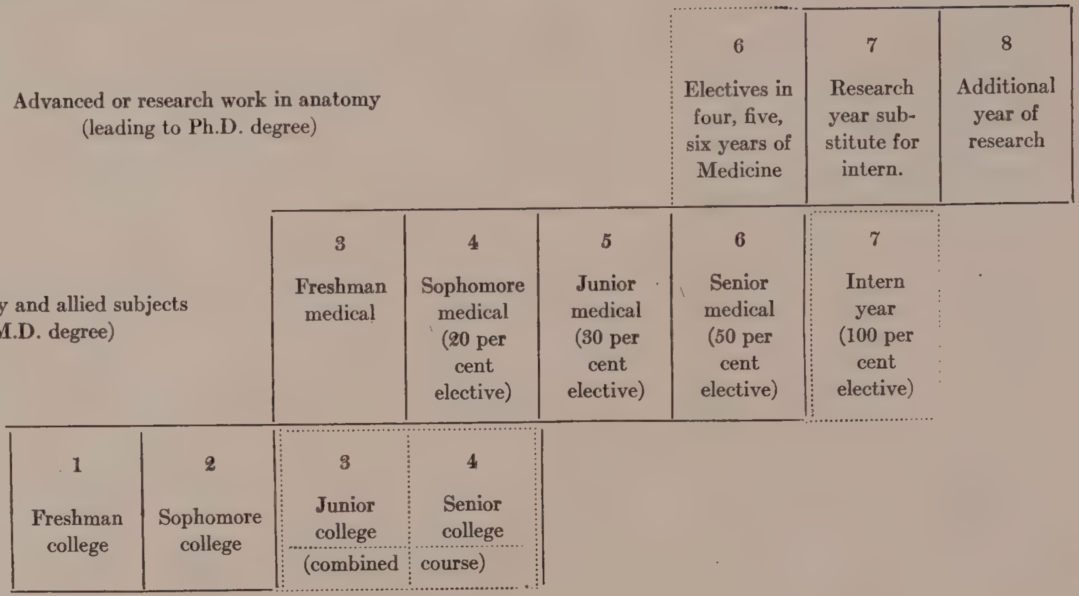
In general, therefore, it may be said that in terms of degrees, the *equivalent* of both the M.D. and the Ph.D. is desirable. So far as the anatomists of the present generation are concerned, however, very few have actually taken both degrees. In most cases, after the general college work, one of two roads has been followed: the medical curriculum leading to the M.D. degree, or graduate work leading to the Ph.D. degree. It so happens that of the present committtee of nine anatomists six followed the former path, and three the latter. What usually happens is that the anatomist with the Ph.D. makes up his deficiency by supplementary study in allied medical work; while the M.D. as a rule finds it necessary to devote himself to additional research work for a considerable period before he becomes a competent anatomist.

Dr. Evans protests strongly against the current tendency to consider the Ph.D. degree as representing a more thorough training in research work than does the M.D. degree. He insists that research work should be made an essential part of the requirements for the M.D. degree, making space in the curriculum for this by reducing the specific requirements (especially in the clinical specialties) and introducing a liberal elective system. While in view of the prevailing conditions in American medical education this may appear a "counsel of perfection" not likely to be realized in the immediate future, many of us would agree that a liberalizing of the medical curriculum in this direction is an outstanding need. The principle of electives in the medical curriculum is already well established to a limited extent in several of the leading medical schools and should be extended to all. This applies especially to the new fifth-year requirement, which may usually be met either by a hospital internship or by a year of research work in any well-equipped medical laboratory. This substitution should always be permitted.

Assuming that the medical curriculum provides liberal electives and adequate facilities for research work, it is of interest to note the probable minimum time within which it would be possible to obtain the training which we have outlined as essential for the anatomist. Table 1 may perhaps make clearer the principal points in this con-

REQUIREMENTS FOR TRAINING IN ANATOMY

Solid lines represent years required for degrees; broken lines, electives.



Advanced or research work in anatomy (leading to Ph.D. degree)						6 Electives in four, five, six years of Medicine	7 Research year substitute for intern.	8 Additional year of research
Elementary anatomy and allied subjects (leading to M.D. degree)			3 Freshman medical	4 Sophomore medical (20 per cent elective)	5 Junior medical (30 per cent elective)	6 Senior medical (50 per cent elective)	7 Intern year (100 per cent elective)	
General college work (leading to B.S. or B.A.)	1 Freshman college	2 Sophomore college	3 Junior college (combined	4 Senior college course)				

nection. The work is classified according to the three grades or stages previously considered. The general college work requires two to four years, the medical work four (or five) years, and the graduate or research work three years. There are two obvious possibilities of reducing the total time by overlapping or "telescoping" in the three grades of work. In the well-known "combined course," the first and second years of medicine may replace the junior and senior years of general college work. Furthermore, if a liberal elective system prevails, it should be possible to obtain practically a year (supplemented perhaps in vacation) of advanced or research work in anatomy during the four years' medical course, and a full year of research in lieu of the internship. An additional (third) year of research work in anatomy would complete the desirable quota, giving in all a training corresponding to the usual requirements for the B.S., M.D., and Ph.D. degrees in a minimum of eight years. This would be possible only under the most favorable conditions, however. Under ordinary circumstances it would be more likely to require nine or ten years before the anatomist could consider himself fully equipped for an independent career. This is particularly true if it has been necessary, for financial reasons, to engage in teaching for more than the minimum amount of time.

The financial or economic aspects of a career in anatomy constitute an important problem whichcan not be ignored. As Dr. Streeter points out, the anatomist in order to acquire an adequate training must make an expenditure of approximately $10,000, and must give eight to ten of his best years. There should be a fair return on the investment. The remuneration to be expected, under present conditions, begins with an instructorship at about $2,000 and leads ultimately to a professorship at perhaps $5,000. In comparison with the financial rewards in the practice of medicine, this is insufficiently attractive. It is generally recognized that conditions must be materially improved or the departments of anatomy (likewise physiology and pathology) will soon deteriorate, to the ultimate detriment of medicine in general.

The unsatisfactory status of the fundamental medical sciences has recently been shown by a committee of the National Research Council[1] and emphasized by Dr. Wilson.[2] The latter endorses, as a possible remedy, Keith's view that laboratory men should be permitted to devote a part of their time to clinical practice, which would increase their income as well as enable them to give more practical instruction to medical students.* Our anatomy committee regards this plan as a reactionary proposal, which would injuriously affect the future development of anatomical science. Better a half-starved full-time anatomist than a well-fed part-time practitioner! Clinical anatomy is a legitimate and desirable field for scientific work; but it should not be required of the anatomist in order to eke out his income by fees from patients. The wise solution of the problem lies rather in the improvement of conditions so as to enable talented men to devote themselves whole-heartedly to anatomical teaching and research. As Dr. Stockard puts it, "The most important object should be to attract men of high ability with the proper hereditary complex, such as now go into medical practice and the business fields."

GRADUATE WORK IN ANATOMY FOR CLINICIANS

The committee recognizes the necessity for further basic work in anatomy by progressive clinicians, and favors coöperation with them by providing so far as possible the necessary facilities. Aside from general practitioners who desire merely brief review work (chiefly in dissection), opportunities should be provided especially for those preparing to specialize in some clinical field, and who desire to make an extensive and intensive study of the anatomy (including histology and embryology) of the regions concerned. As a rule, this does not require the organization of additional courses, but merely the opportunity for individual work, under supervision on materials already available in the laboratory. This should culminate in research work on anatomical problems in which the clinician is especially interested. In some cases it may be desirable to add to the anatomical staff, as part-time or full-time members, some of the younger clinical specialists who are willing to devote time to the development of this work in teaching, making special preparations, and so forth. Such work in clinical applied anatomy

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*That the committee has misunderstood this proposal is evident from the following statement in a letter from Dr. Wilson to the Chairman of the committee: "I have gone carefully over my article on 'The Present Status of Preclinical Branches,' and I am at a loss to see how you could have interpreted my statements or the quotation from Keith as suggesting that preclinical men should engage in private medical practice. Keith says: 'At *medical schools* they should hold clinical appointments.' I say: 'Should not the *University Hospital* provide contact with patients?' We both suggest that such clinical contact will make the man a better teacher of future practitioners of medicine and that his ability to meet the clinician on the latter's own ground will gain him greater respect. But surely, both these are far from the 'straw' anatomist-practitioner, which the report of your committee so valiantly disposed of."

should be fully encouraged, and should lead to results worthy of publication.

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TEACHING THE FUNDAMENTALS OF SURGERY FROM THE VIEWPOINT OF THE GRADUATE SCHOOL*

LOUIS B. WILSON

The Committee on Graduate Instruction in Orthopedic Surgery appointed by the Council on Education of the American Medical Association last year made certain fundamental suggestions concerning the training of orthopedic surgeons. The first paragraph of that report† is as follows: "This Committee takes the position at the outset that orthopedic surgery is a branch of general surgery and that no preparation for the practice of orthopedic surgery can be considered satisfactory which does not comprise adequate practical training in the principles and technic of general surgery." This very wise resolution no doubt explains why the chairman has asked me to talk on "the teaching of surgery" rather than on "the teaching of orthopedic surgery." What I have to say will relate to unorganized graduate medical training, to our experience in organized graduate work in the University of Minnesota, and to the lessons which may be drawn from that experience.

UNORGANIZED TRAINING

Unorganized graduate training in surgery and other special fields of medicine is, of course, no new thing. In this country until recent years most of it has been accomplished in internships, residencies, assistantships, and apprenticeships, supplemented in some instances by short courses in so-called postgraduate schools either here or abroad, by visits to other clinics, and so forth. We must not forget that this unorganized, somewhat hit-or-miss system has been the chief factor in the development of the present-day leaders in all the special fields of medicine. It has many advantages, especially in that it permits the greatest freedom of choice on the part of the graduate student who desires to fit himself for practice in a special branch. Some of its disadvantages are as follows:

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* Reprinted from the Journal of the American Medical Association, 1922, lxxix, 120–125. From the Mayo Foundation, Rochester, Minnesota.

† American Medical Association Bulletin, July, 1920, xiv, No. 1, 45–49.

1. The system is apt to waste the time of the graduate student. This ill-spent time apparently averaged more than a year for each of 217 leaders in special clinical fields who responded to questionnaires of the Committee on Graduate Medical Education of the American Medical Association two years ago.*

2. Students in Surgery left to their own devices are apt to strive for technical training before they have grasped the essential relationships of pathology, or have attained sufficient skill in surgical diagnosis. Even their technical training may be too narrow to produce broad-gauge surgeons or orthopedists.

3. Interns, residents, and assistants are too often selected from among the graduates of the school with which the hospital is connected. These young men, without experience elsewhere, may acquire only very provincial viewpoints and are apt in turn to become members of their medical school faculty. The result of this inbreeding has already shown itself in some medical faculties in early professional paresis.

4. The failure of universities in the past to recognize by higher degrees standard attainments in special medical fields has resulted in the attempt to remedy this by such organizations as the American College of Surgeons and the American College of Physicians, which, though actuated by the best of intentions, must labor under great difficulties in any attempt to standardize large numbers of widely scattered applicants of whose actual attainments they can have only the most superficial knowledge.

MINNESOTA'S EXPERIENCE

With some realization of the difficulties mentioned in unorganized graduate medical training, the University of Minnesota seven years ago undertook to reorganize the opportunities in its laboratories and university-controlled hospitals in Minneapolis and St. Paul, and in the laboratories and hospitals of the Mayo Clinic in Rochester, Minnesota, into a system which would provide means for selected graduate students, under advice of a competent faculty, to round out any existing weak points in their previous medical training and to fit themselves on a broad educational basis for practice in special clinical fields, including surgery and orthopedic surgery. Accordingly, a plan for graduate medical education which in general follows that in operation in many universities for graduate work in the liberal arts and the other sciences was formulated and has been in operation since January 1, 1915. Selected graduates of class "A" medical schools who have had at least one year of graduate internship or laboratory work are accepted for periods of from three to five years of graduate work in a specific field. Our seven years' experience, so far as statistics go, may be summarized thus:

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* American Medical Association Bulletin, July, 1920, Vol. 14, No. 1, pp. 45–49.

At present more than 1,000 prospective candidates a year are seeking opportunities for graduate medical training in the Mayo Foundation which is one division of the medical graduate department of the graduate school of the University of Minnesota. Of these about 60 per cent are inquiring for work in general surgery. Almost all of the remainder are seeking opportunities in other clinical fields. An exceedingly small number are seeking opportunities in the preclinical branches.

Of the 1,000 prospective students a year, many are discouraged at the outset by the small number of vacancies in fellowships available, by the long period of work required, or by the stringent educational requirements for entrance and graduation. However, about 200 a year do complete their formal application for a three- to five-year service, including submission of their credentials, references, and so forth. In all, 1,005 such complete formal applications have been filed in the Mayo Foundation. A careful analysis of these applications shows that 778 candidates were eligible and 227 ineligible for admission under the rules of the University. Four hundred eighteen students have been accepted, of whom 184 have selected surgery and eight, orthopedic surgery as their major field. All students in orthopedic surgery have, of course, taken work in general surgery and many students in general surgery have had special work in orthopedic surgery. Hence it is proper to consider these two groups together. Of these 192 students in surgery, seventy-two are either now on duty in the Mayo Foundation or have been appointed for service during 1922. Twenty-four students in surgery were permitted to resign during the first year of the fellowship, seventeen during the second year, and forty-two during their third year or later, without having attempted to meet the final requirements for advanced degrees. Five more are now on leave of absence. Up to the present time, including the graduating class for June, 1922, thirty-seven candidates have attempted to meet the final requirements for

TABLE 1

GRADUATE STUDENTS IN THE MAYO FOUNDATION FROM JANUARY 1, 1915 TO MAY 16, 1922

Major field.	Graduate students now here or appointed July 1, 1922.	Left during first year of fellowship.	Left during second year of fellowship.	Left during third year or later, not candidates for degrees.	Now on leaves of absence.	Applied for degrees.	Received M. S. degree.	Received Ph.D. degree.	Failed.	Total number graduate students (duplicates omitted).	Additional eligible applicants not accepted.	Total eligible applicants.	Ineligible applicants.	Total completed applications.
General surgery	65	24	17	41	5	36	30	2	4	184	246	430	148	578
Orthopedic surgery	6	..	..	1	..	1	1	..	..	8	5	13	3	16
Urology	6	3	4	2	1	5	5	..	..	20	8	28	7	35
Ophthalmology	4	6	1	1	..	..	..	..	..	12	2	14	5	19
Eye, ear, nose, and throat	...	..	..	..	..	..	..	..	..	...	6	6	15	21
Otolaryngology	10	2	5	1	1	2	2	..	..	20	6	26	5	31
Medicine	47	9	3	5	2	7	5	1	1	72	42	114	30	144
Dermatology	6	2	..	..	1	1	1	..	..	9	4	13	...	13
Pediatrics	3	2	..	..	..	..	..	..	..	5	3	8	2	10
Neurology	4	..	..	..	..	..	..	..	..	4	3	7	...	7
Roentgenology	5	2	..	..	..	..	..	..	..	7	4	11	4	15
Pathology	9	4	2	..	..	5	4	1	..	18	7	25	5	30
Bacteriology	1	1	1	2	..	2	1	1	..	7	10	17	...	17
Chemistry	3	2	1*	..	..	1	1	..	..	6	4	10	...	10
Physiology	...	..	..	..	..	..	..	..	..	...	2	2	...	2
Dental surgery	9	2	1	..	..	..	..	..	..	12	8	20	3	23
Total	178	59	35	53	10	60	50	5	5	384	360	744	227	971
Short term†	1	33	..	..	..	..	..	..	..	34	...	34	...	34
Total	179	92	35	53	10	60	50	5	5	418	360	778	227	1005

* Died.

† Medical officers from the United States services, fellows from other universities, appointees of foreign governments, et al. Does not include undergraduate volunteer summer students.

advanced degrees in surgery. Of these, thirty-one have been granted the degree of Master of Science in Surgery, two, the degree of Doctor of Philosophy in Surgery, and four applicants have failed to meet the requirements for any advanced degree in surgery.

These facts and certain others which may be of interest concerning other fields will be found in the table on page 664.

Our experience during the last seven years in interviewing and corresponding with several thousand prospective graduate medical students, and in working daily with the four hundred who have been with us, has led us to make certain observations concerning the previous training of the applicants, concerning various means of giving those who are accepted opportunities of becoming competent in their chosen fields, and the means of testing their attainments.

DEFECTS IN PREVIOUS TRAINING

1. Applicants for fellowships average about twenty-seven years of age at the completion of their internship, which averages about one and one-fourth years. This is obviously too old. Allowing eight years for college, medical school, and internship their average age at leaving high school was about nineteen years. From personal interviews with hundreds of applicants I am convinced that their retardation usually has been in the high school, and there, almost always through difficulty with algebra, geometry, and foreign languages. All of these studies, I believe, are customarily begun after the passing of the optimum psychologic period for their acquisition. I doubt very much whether eight years of age is too early to begin the study of modern foreign languages and I believe that every day after twelve years of age that such study is postponed adds an unnecessary burden to the student. There is no question but that a child of twelve can readily grasp the fundamental principles of geometry and algebra. The postponement of the teaching of the principles of these until arithmetic is nominally mastered is an error which results in unnecessary hardship for the student in later years.

2. Very few applicants have a real reading knowledge of French or German despite the fact that they have nominally met the class "A" medical school requirements in this respect. This is the result of poor teaching of the languages and the failure of medical school faculties to see that the medical student is required to persist in his reading of foreign medical literature.

3. Many applicants use incorrect spoken and written English. Many of them apparently have little knowledge of those subjects which contribute to good citizenship and personal culture, such as history, economics, literature, art, and music. Defects in these probably may be charged to their homes as much as to their schools.

One cannot help believing that all such defects might be readily remedied. Attention in the home to the use of correct English, to the reading of good books rather than sloppy juveniles, to training in habits of industry, persistence, promptness, honesty, and courtesy should lay the foundation. If, then, the grade and high schools would provide for those whose parents desired it, instruction in algebra, geometry and foreign languages at the period when these can best be learned it should be possible for most boys and girls to enter college at sixteen years of age. Added to this a four-year college course which includes at least as much study of the humanities as of physics, chemistry and biology, should bring the twenty-year-old college graduate to the portal of the medical course not only with more culture than he has at present, but also with much more ability to evaluate and assimilate the important portions of the several preclinical medical sciences with which he is deluged during his first two years in medical school.

The attempt to teach, in the first two years of medical school, six complete medical sciences, any one of which would require the full attention of the medical student for at least two years were, he fully to grasp the subject, is probably responsible for the next defect to be mentioned.

4. Many applicants have but a very superficial knowledge of anatomy, biochemistry, physiology, pathology, bacteriology, and pharmacy. Their knowledge of essentials is as superficial as their knowledge of unessentials.

We must either double the time now allotted to the teaching of the preclinical medical sciences, or we must halve the amount of subject matter in each which we attempt to teach if we are to approach necessary thoroughness in the essentials in these subjects.

5. Many present-day graduates are at a loss to apply what they do know of the essential principles of the preclinical branches in the diagnosis and treatment of disease. Unfortunately, the attitude seems to exist to some extent that at the end of the first two years in the medical school, when the examinations in anatomy, pathology, chemistry, physiology, bacteriology, and pharmacology have been taken and passed,

the student is through with these subjects for the rest of his life, and now, that he is no longer to be bothered with them, he may give his attention to the really interesting fields of clinical medicine. This attitude is so pronounced that there is a strong tendency in the last two years of medical school and during internship to permit the student to fail to apply his knowledge of the fundamental facts of the preclinical branches in his study of the diagnosis and treatment of disease.

The physician who has a sufficiently thorough knowledge of the essentials of the fundamental medical sciences to use them as familiar tools in the every-day study of complicated individual cases, and who threads on these lines of knowledge his careful clinical observations until he can reach a correct diagnosis, and formulate a logical plan of treatment, is unfortunately getting rarer and his production, we believe, is not favored by the present cramming system in our medical schools.

SELECTION OF FELLOWS

However, with all his defects, the present-day applicant for graduate medical training is usually a very likeable and enthusiastic chap. On the assumption that the limited opportunities for high grade graduate training should be given only to high grade students most likely to profit by them, how shall we determine whether a certain applicant has the makings of a real surgeon within him? A large number of young medical students think they have such ability. They are attracted toward surgery because it is the spectacular side of medicine. They feel that they have a "call" to surgery. This insistance of a "call" on their part we should not take too seriously. Dogs of most every breed will hesitate or stop at the sight of a wild animal; but if we mistake this common hesitation for pointing and try to train a bulldog for hunting prairie chickens or quail we waste our time. Similarly, if we try to train every medical student who thinks he is a born surgeon we will waste our time, his time, the patient's time, and occasionally the patient's life. For this reason I doubt whether courses in the graduate school leading to the study of special fields in medicine should be thrown open unqualifiedly to every student who is able to pay a tuition fee. While the judgment of faculties may be poor, they are in the long run probably much better than the ungauged desires of the average medical student who seeks admission to a graduate school for the purpose of becoming a surgeon. In making selections, however, we must not be guided entirely by scholarship as recorded in the medical school and college. We must look for evidence of broader scholarship than these institutions now furnish. True, his scholarship in medical school should have been at least sufficient to place the candidate in the upper third of his class. But most of all we should try to get some estimate of the applicant's character. Unless he shows in his personal appearance, in his manner with his associates, in his manner with patients (especially poor patients), in his general demeanor, in his honesty, his loyalty, and in his manner of receiving criticism that he is at heart a courteous gentleman, he should not be encouraged to enter an already overcrowded field of medicine. If, in addition to these qualifications he has ambition, initiative, industry, persistence and promptness, he is worthy of careful consideration for training.

The candidate having been selected and means provided, either from his own funds or from private benefaction, for him to continue his special study for a period of not less than three years and preferably five, how shall his time be spent?

SERVICES IN WHICH THE CANDIDATE SHOULD BE TRAINED

Necropsy service.—At the beginning something must be done to attempt to patch up the defects in his previous training. Not all of this patching can be done at once nor should it be. It is better to distribute repairs as required throughout his three to five years of training. One important phase of his education has been almost always neglected in American schools; he has not had his hands in more than half a dozen necropsies. I firmly believe that no man should be permitted to operate on the living until he has operated at autopsy on at least one hundred dead. Our first duty then, if possible, is to place the embryo surgeon where he can make a start in necropsy work which, if he is to be successful, he will need to follow out for the remainder of his professional life.

At the necropsy the student should actually make the section, beginning first as junior, acting as assistant, and later as senior, making the postmortem. All of this work should be done under the eye of a competent pathologist who as a measure of restraint may need to tie his own hands behind his back. The instructor must remember, however, that the embryo surgeon had better make errors on the dead than on the living. How a sufficiently large necropsy service is to be developed even in large hospitals is, I believe, merely a question of going after permissions in a straightforward but persistent manner. Time and time again we have had demonstrations in the United States that if we want postmortems we can get them. No hospital should be satisfied with performing necropsies on less than 75 per cent of the bodies of all patients that die. Friends of the dead have as much right to demand this service as the profession has to request permission to render it. The percentage of postmortems in an institution and the character of and attendance on clinic-pathologic conferences are perhaps the surest index of the scientific work of the institution.

Diagnostic service.—After the necropsy service the next in which the graduate student should be placed is the diagnosis of disease. Here, under constant competent supervision, the graduate student should have an opportunity to take histories, make the simpler laboratory examinations, and designate more complicated cases for all classes of patients. The service should not be confined to cases that have already been separated into medical and surgical. The entire "grist" should be seen. In this work the most important point to be looked out for by the instructor is that the graduate student shall be compelled in his analyses of cases to give his reasons in terms of anatomy, physiology, pathology, and so forth, that he may have constantly before him the necessity for applying the principles of these subjects in his interpretation of clinical phenomena and in his final summary or diagnosis. Throughout this work and all of his subsequent work the graduate student should be expected to attend necropsies on at least all patients that die with whom he has come in contact and all clinic-pathologic conferences occurring in the institution.

Operative service.—After not less than one year of this service the embryo surgeon may be placed on duty as second assistant in the operating room where his duties include the hospital preparation of patients for operation, his ordinary duties as second assistant, and the postoperative care of patients.

As soon as his skill has sufficiently developed, which should be in not less than six months and ordinarily at the end of one year, he should be given a first assistantship. In our experience in the Mayo Clinic these first assistantships are of most value to the student if they extend for a period of not less than one year under the same chief surgeon. Fellows may be reappointed for a second year. The student's service here may include duties outside the operating room, similar to those he had as second assistant, and in addition he becomes to some extent responsible for the training of his junior. As soon as he gives evidence of sufficient ability he should be given opportunity to act as chief surgeon at operations while the surgeon actually in charge stands by and sees that he does his work properly and that no harm comes to the patient.

The work as thus outlined represents the principal opportunities for study which should be provided for the graduate student in surgery. Nothing has been said about class work, lectures, quizzes, examinations, theses, degrees, and so forth, However, these all enter in their proper place.

Lectures.—I very much doubt the value of the formal routine lecture course for graduate medical students. Its purpose may be better served by proper guidance in suggestive reading courses, in clinical conferences or seminars held not less frequently than once a week, and in inspiring lectures from outside men who have done special pieces of work and who may be induced to come and deliver lectures concerning it.

Seminars.—The seminar or clinical conference provides the best opportunity for teaching graduate medical students. This is not so when the professor in charge does all the talking. His function should be to answer questions rather than ask them; to stimulate discussion rather than to dominate it. In other words, he should encourage his young men to form opinions and to express them, thus giving him an opportunity for kindly criticism. The spirit of the seminar should be one of coöperative study rather than of master and pupil. The seminar and conference should be held at a definite period of from one to two hours, not less than once a week throughout the entire course.

Quizzes.—How shall we know whether the graduate is making real progress? Principally by intimate, daily intercourse with him. It is desirable when men are admitted from many different institutions, in order to test the efficiency of one's standard of admission, and to be sure that the men selected really have some knowledge of those principles of fundamental medical sciences which underlie clinical medicine, to give an examination to each man early in the course. This examination preferably should be oral, should be taken part in by three to five members of the faculty, most of whom should be clinicians, who should quiz the candidate very thoroughly, yet avoid all questions except those designed to determine whether he has knowledge of the absolutely essential principles in the fundamental medical sciences. The candidate who is found not to have such a knowledge should not be permitted to continue with his work. It is not the place of the graduate school to

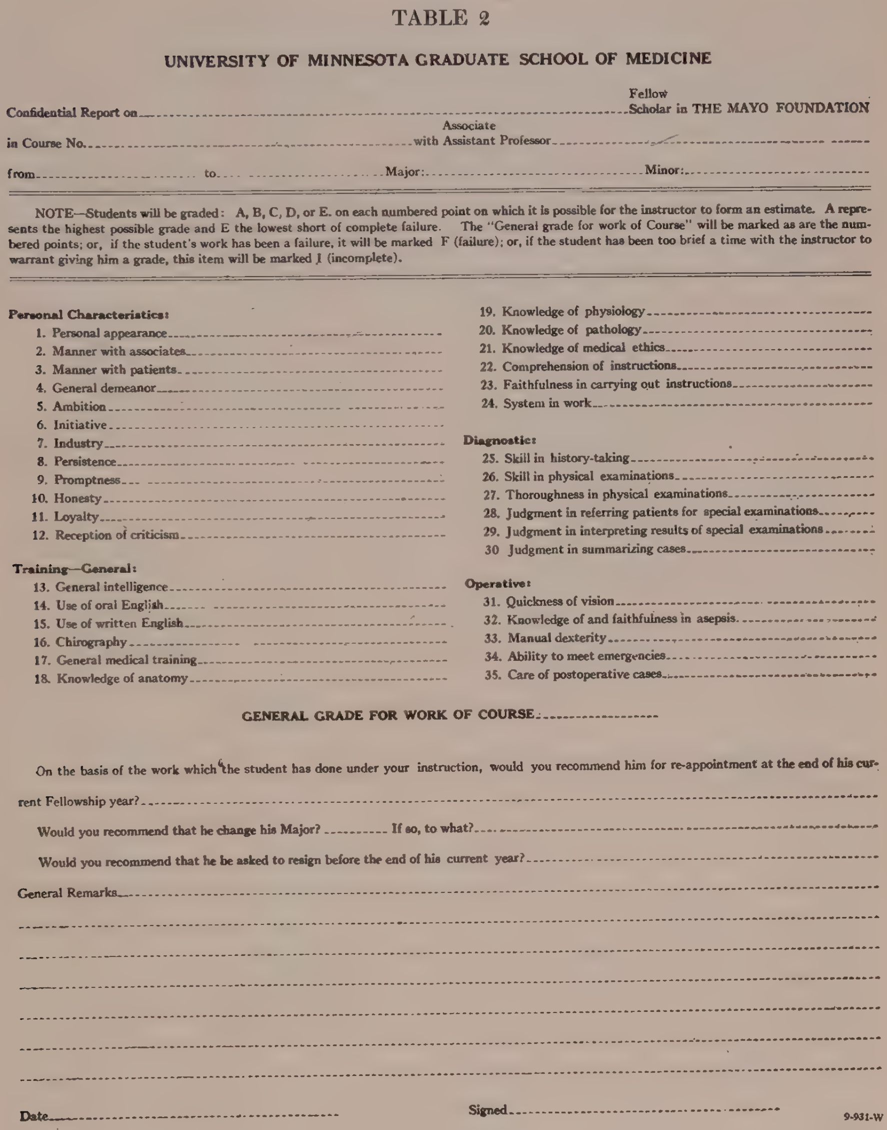

TABLE 2

UNIVERSITY OF MINNESOTA GRADUATE SCHOOL OF MEDICINE

Confidential Report on ______ Fellow / Scholar in THE MAYO FOUNDATION

in Course No. ______ with Associate / Assistant Professor ______

from ______ to ______ Major: ______ Minor: ______

NOTE—Students will be graded: A, B, C, D, or E. on each numbered point on which it is possible for the instructor to form an estimate. A represents the highest possible grade and E the lowest short of complete failure. The "General grade for work of Course" will be marked as are the numbered points; or, if the student's work has been a failure, it will be marked F (failure); or, if the student has been too brief a time with the instructor to warrant giving him a grade, this item will be marked I (incomplete).

Personal Characteristics:

1. Personal appearance ______
2. Manner with associates ______
3. Manner with patients ______
4. General demeanor ______
5. Ambition ______
6. Initiative ______
7. Industry ______
8. Persistence ______
9. Promptness ______
10. Honesty ______
11. Loyalty ______
12. Reception of criticism ______

Training—General:

13. General intelligence ______
14. Use of oral English ______
15. Use of written English ______
16. Chirography ______
17. General medical training ______
18. Knowledge of anatomy ______
19. Knowledge of physiology ______
20. Knowledge of pathology ______
21. Knowledge of medical ethics ______
22. Comprehension of instructions ______
23. Faithfulness in carrying out instructions ______
24. System in work ______

Diagnostic:

25. Skill in history-taking ______
26. Skill in physical examinations ______
27. Thoroughness in physical examinations ______
28. Judgment in referring patients for special examinations ______
29. Judgment in interpreting results of special examinations ______
30. Judgment in summarizing cases ______

Operative:

31. Quickness of vision ______
32. Knowledge of and faithfulness in asepsis ______
33. Manual dexterity ______
34. Ability to meet emergencies ______
35. Care of postoperative cases ______

GENERAL GRADE FOR WORK OF COURSE ______

On the basis of the work which the student has done under your instruction, would you recommend him for re-appointment at the end of his current Fellowship year? ______

Would you recommend that he change his Major? ______ If so, to what? ______

Would you recommend that he be asked to resign before the end of his current year? ______

General Remarks ______

Date ______ Signed ______ 9-931-W

Fig. 247.

teach the elements of preclinical branches, but to give opportunity for the daily use of those elements.

Course records.—That some record may be kept of the work of the graduate student it is necessary that the faculty member with whom he is working shall make a report of his work in all respects from time to time, preferably at the end of each quarter. This report should be confidential to the dean of the school and should cover not only an estimate of the details of his diagnostic and operative skill but also of his general training and his personal characteristics. Such a rating sheet which has been in use in the Mayo Foundation and previously in the Mayo Clinic for a number of years is presented on page 671.

If the ordinary university grades of A, B, C, D, and so forth, are used it is a good rule that no student receiving a grade below that of B shall receive credit toward his degree for the work so graded. It would seem to be a fair rule also that any student receiving for two consecutive periods a general grade of D or lower should be requested to leave the institution. Opportunities for graduate study of medicine on a university basis are altogether too few in this country to warrant their being wasted on mediocre and inferior men.

Examinations.—Since our present system of licensing practitioners in the various states of the United States is based entirely upon examinations we are under the necessity of giving examinations to graduate students if we are to send them out from the university with the university stamp upon them. As a result all graduate students who are candidates for degrees from the university should take examinations, both oral and written, and these should be more severe in the fields of the candidate's major and minor subjects than he is ever going to get anywhere else.

STANDARD FOR DEGREES

Aside from a satisfactory residence of a definite period which should be from three to five years for the graduate study of surgery, a satisfactory record of which has been filed at definite intervals, and aside from the passing of the examinations herein suggested, what other requirements should be made of a prospective candidate for a graduate degree in surgery from a university before he may be properly recommended for that degree? In the first place, it would appear that he must be competent in his field; in other words, he must be an "honest-to-goodness" surgeon. The only way this can be determined as a matter of record is on certificate from the surgeons with whom he has worked that in an emergency they would be willing to send members of their own families to him for diagnosis and surgical treatment. If they are not willing to certify to the candidate's competence to this extent the university should not grant him an advanced degree in surgery, since the granting of this degree will stamp the candidate as a surgeon competent to care for citizens of the state.

A further qualification should be that the candidate has shown that he has a scientifically trained mind, that he is capable of analyzing and synthesizing his own observations, either clinical or experimental, or both, comparing them with those of other men doing similar work and drawing logical conclusions therefrom. Though in many respects unsatisfactory, the production of a thesis which embodies such an analysis is perhaps the best means we have for the candidate to demonstrate his scientific ability in this respect.

One of the most important services that an institution should provide is that of careful revision by members of the faculty of all articles written by graduate students. Besides criticising these for their truthfulness, accuracy, clearness, and so forth, they should be carefully edited by a competent editor, who then laboriously explains to the writer the reasons for the changes made. The state of our medical literature at present is most deplorable. It will not be better until we give it more thorough and more constant attention. The undergraduate medical schools should do this work; the graduate medical schools must do it.

SUMMARY

The graduate of a class A school who has had a minimum of one year's internship in a general hospital, who has had three to five years' opportunity for graduate work in surgery which has included at least six months of necropsy service, one year of diagnostic service, and at least one and a half or, better, two and a half years of operative service, during all three of which services he has had constantly before him the necessity for using daily the essential underlying principles of anatomy, physiology, chemistry, pathology, bacteriology, and pharmacology until they have become to him absolutely familiar tools for the diagnosis and treatment of disease, who is above all a competent surgeon, who has passed more severe examinations in the field of surgery than he will ever be obliged to pass elsewhere, and who has prepared and defended a thesis of the character indicated, may properly be recommended for the degree of master of science in surgery or master of science in orthopedic surgery, as the case may be, to be granted by a properly constituted university of which the medical school is a part.

Besides the foregoing it sometimes happens, though unfortunately not often, that a graduate medical student shows that he has real research ability and demonstrates this beyond peradventure by making an actual contribution of considerable import to medical science. For such a student there should be reserved the degree of Doctor of Philosophy in surgery or orthopedic surgery. Of course in additiom to the requirements outlined for the degree of Master of Science he should fulfill also those other minor conditions, particularly in relation to foreign languages, which are ordinarily required by universities of candidates for the degree of Doctor of Philosophy in other fields.

CONCLUSIONS

In conclusion, I wish to urge the importance of graduate work in surgery, orthopedic surgery, or any other specialty, being done in institutions where work in other fields of medicine is going on at the same time. Isolation in the long run is a serious handicap.

The daily association of men who are engaged in other fields, the discussions with them in informal conferences, and especially the frank criticisms of each other in staff meetings at which are read the articles which are the results of scientific study in the institution, all conduce to a much broader view of a specialty and of the making of much broader men who are to practice in the specialty.

XI

TECHNIC

A TECHNIC FOR THE ESTABLISHMENT OF A PERMANENT PANCREATIC FISTULA WITH THE SECRETION OF INACTIVE PROTEOLYTIC FERMENT*

WILLIAM DeP. INLOW

Few methods which have been used for the establishment of permanent pancreatic fistulas in animals have been entirely successful and none, ideal. Following the principle of transplantation of the duodenum under the skin, as developed by Mann in establishing biliary fistulas, the following technic, evolved for the formation of pancreatic fistulas, seems to offer certain advantages over those heretofore suggested.

A curved incision about 10 cm. long is made through the skin of the abdomen starting just below the xiphoid process and circling to the right until at its middle the cut is approximately 2 cm. from the middle line. This curved skin flap, with sufficient of the underlying subcutaneous tissue to insure adequate blood supply, is reflected to the linea alba and the ordinary laparotomy incision is made. The duodenum is delivered into the wound and turned to the right. The blood vessels in the immediate neighborhood of the entrance of the major pancreatic duct into the intestine are ligated and severed, the pancreas is separated from the duodenum in this region, and the duct itself isolated. The transplantation of the duodenum is accomplished by rotating its axis to the right, and approximating the two edges of the abdominal wall under the duodenum by means of four single mattress sutures which include both fascia and peritoneum. Openings just sufficient for the duodenum to pass through snugly, but without constriction, are left at the upper and lower ends of the wound. In the rotation of the duodenum a small portion of the pancreas is brought out of the abdomen and thereby the entrance of the duct into the gut becomes very superficial. The mattress sutures pass through this portion of the pancreas in an oblique direction. The head of the needle is passed first in order not to injure blood vessels by the sharp point, and comes out at the juncture of the intestine and the right layer of the mesoduodenum. At each of these points a portion of the bowel wall is included in the sutures for secure anchorage. The sutures are tied and the abdominal cavity shut off from the field of operation (Fig. 248).

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* Paper published in full in the Journal of Laboratory and Clinical Medicine, 1921, vii, 86–90. From the Section on Experimental Surgery, Mayo Clinic.

The skin on the right of the initial incision is reflected in its central portion and the duodenum brought over the right and fitted into the cavity thus made. Catgut sutures passing through the peritoneal muscular coats of the intestine and through the superficial fascia of the abdominal wall are inserted to maintain the bowel in its new position. The pancreatic duct is dissected free for the short distance which it runs obliquely beneath the serosa of the gut, and is partially severed at the point where it enters the muscular layer. A very fine silk suture on a small needle is passed through the free left lip of the duct, a section of a ureteral catheter is inserted into the canal for a short distance, and the duct completely severed. The serosa is brought together over the small wound in the intestinal wall by one or two Lembert sutures. Three other fine silk strands are then passed through the extremity of the severed duct at equal distances, a small stab wound is made in the original semicircular flap of skin just over the point where the duct disappears into the pancreas and the duct with the catheter is brought through the opening. The original skin incision is closed by suturing the subcutaneous fascia with catgut and the skin with interrupted linen stitches. The end of the duct is everted and securely fastened to the skin by means of the four silk sutures, the catheter is left in place and its

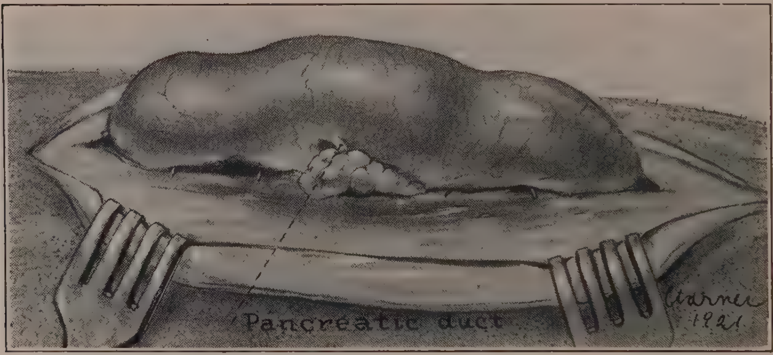

FIG. 248.—The duodenum transplanted outside the abdominal cavity with the major pancreatic duct still in situ preparatory to the establishment of the fistula.

free portion allowed to run along the abdominal wall for from 4 to 5 cm., where it is fastened by two or three superficial stitches. The wounds are iodinized and covered with collodion dressings (Fig. 249).

If the time can be spared a two-stage method is preferable, since the animal may then be in good nutritive condition before the establishment of the fistula, and the chances of peritoneal infection are lessened. At the first operation the duodenum is transplanted under the skin and a month later, at the second operation, the duct is brought to the surface.

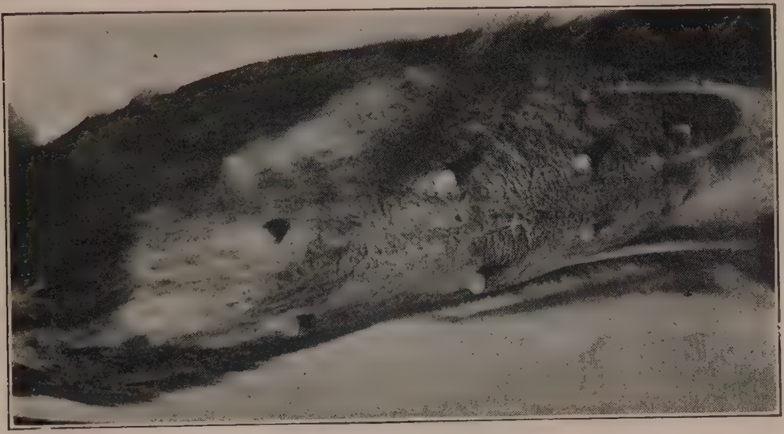

Fig. 249 (E130).—Photograph of dog taken twenty-three days after a one-stage operation for the establishment of a pancreatic fistula. The orifice of the pancreatic duct, bulging due to the transplanted duodenum, and the intact condition of the skin of the abdomen are shown. The animal was killed by ether three months and three days after formation of the fistula and the pancreas grossly was found to be normal.

The success of the technic suggested depends on the following factors: the avoidance of opening the intestine; the fixation immediately under the skin of the point of exit of the duct from the pancreas; and the bringing of the duct to the surface of the abdomen through an incision other than the operative incision. Thus are avoided the danger of peritonitis and stricture of the duodenum, retraction and necrosis of the duct from tension, and subsequent closure of the fistular orifice by its inclusion in the operative scar, factors which are most inimical to success.

METHOD OF DIVIDING THE URINARY BLADDER FOR EXPERIMENTAL PURPOSES*

JAMES A. H. MAGOUN, Jr.

During the investigation of various phases of the problem of infection of the urinary tract, the possibility of dividing the bladder into two portions, each in normal relation to its ureter, presented itself.

Female dogs kept under constant ether anesthesia were used. Aseptic technic was observed in all experiments. A low right rectus incision was made and the bladder isolated and packed off with gauze pads. Two stay sutures were placed in each side of the bladder and the organ was divided down its anterior wall into the urethra (Fig. 250).

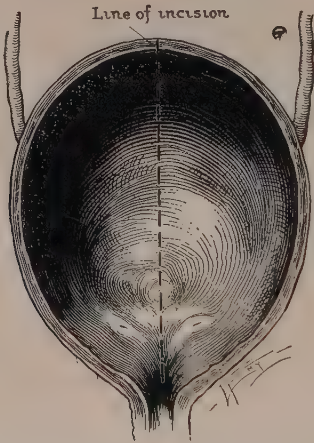

Fig. 250.—Line of incision for division of the bladder.

The ureteral openings were identified and a No. 5 ureteral catheter was introduced through each into the pelvis of the kidney. The posterior wall was then divided midway between the ureteral openings as far as the anterior had been divided. A soft rubber No. 10 French catheter

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* Reprinted from the Journal of Laboratory and Clinical Medicine, 1923. From the Section on Experimental Surgery, Mayo Clinic.

was placed into each side of the divided bladder and brought out of the external urethra. The respective ureteral catheters were then led through the urethral catheter to the external urinary opening (Fig. 251). The two segments of the bladder were closed over these catheters with two running sutures of No. 0 catgut. The surrounding fat was sewed over the lower portion of each segment (Fig. 252). The catheters were held in place by a few sutures of catgut just within the labia and were removed in from twenty-four to forty-eight hours. These catheters were advantageous in three ways: (1) as a means of identifying the ureter, (2) as a guide over which to sew the wall of the bladder, and (3) as a means of keeping the newly formed segments of the bladder empty.

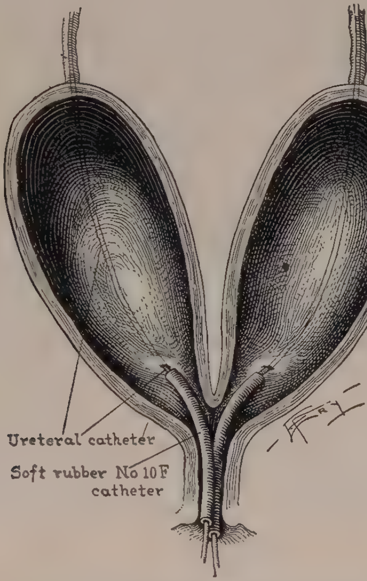

FIG. 251.—Operation completed. Bladder divided and catheters placed in ureteral openings and urethra.

The divided bladder permits the study of its cavity in normal relation to the ureter and kidney. Thus, one of the segments may be infected and the changes in the corresponding kidney and ureter may be noted. If obstruction to one segment below the entrance of its ureter is produced, the effect of obstruction at the outlet of the bladder may be studied. It is also possible by this means to study the comparative physiology of the two kidneys. The results of sudden decompression of the chronically distended bladder are now being observed by this method under the direction of the Sections on Urology and Experimental Surgery.

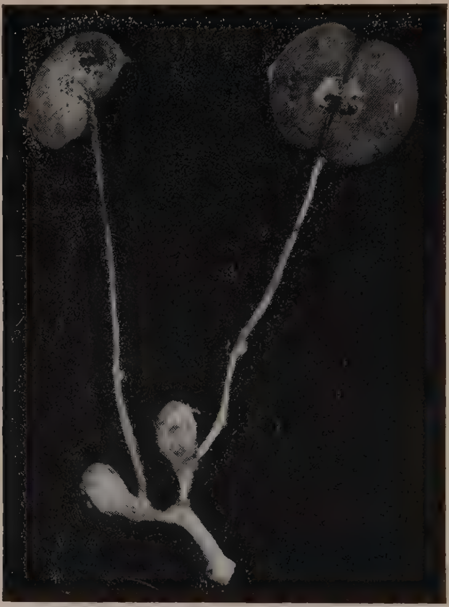

FIG. 252.—Divided bladder, urethra, ureters, and kidneys two months after operation.

It is suggested that this method of placing catheters may be of some value in resections of the bladder in man.

A SUCTION APPARATUS FOR THE TREATMENT OF EMPYEMA*

JOHN W. SNYDER

The need for a practical type of suction apparatus to be used in the treatment of empyema prompted me to make a device which is simple, readily constructed, and meets the requirements of daily use.

Negative pressure is produced by a common hydraulic suction pump procurable from any instrument dealer. The type we have used (Fig. 253) has a thick rubber ring in one end (Fig. 254, A) which may be readily attached to any type of water faucet by pushing the ring firmly up around the outlet of the faucet. This obviates special plumbing fittings and permits transportation of the apparatus from room to room. Attaching or detaching the pump requires but a moment's time.

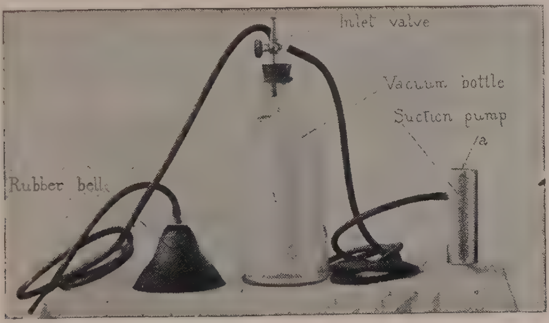

Fig. 253.—Suction apparatus assembled.

A large bottle with a rubber cork containing three perforations is used as a negative pressure chamber and as a receptacle for aspirated fluids (Fig. 253). Metallic or glass tubes are passed through two of the perforations in the cork, one tube (Fig. 254, A, 1) reaching just through the cork and the second (Fig. 254, A, 3) for some distance into the bottle. Through the third perforation an inlet tube having two valves is passed

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* Reprinted from Surgery, Gynecology, and Obstetrics, 1921, xxxiii, 568–569. From the Section on Thoracic Surgery, Mayo Clinic.

(Fig. 254, A, 2). The upper valve is automatic in action, working against a spiral spring. The tension of the spring may be varied by means of a thumb screw. The second valve placed below the spring valve may be used to cut off the inlet tube from the vacuum chamber when desired.

The third part of the apparatus is a soft rubber bell which is to be applied to the chest. Such a bell can be obtained from a device used by plumbers. It consists of a ball mounted on a handle, and all that we found necessary in adapting it to our uses was to remove the handle and drill a hole through the base of the bell into which a tube is fitted.

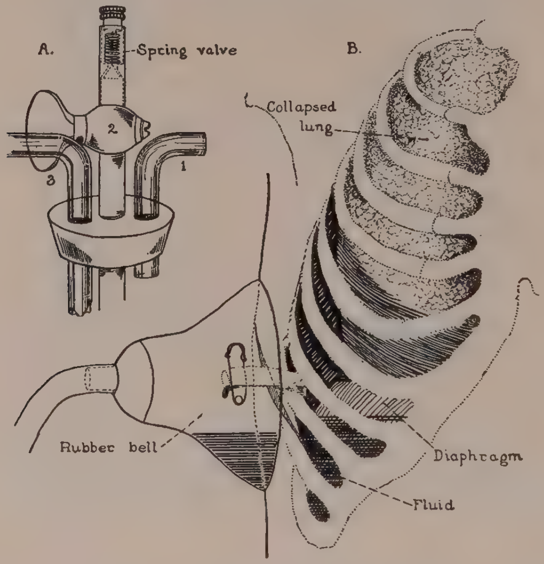

Fig. 254.—A. Detail of inlet valve. B. Bell applied to thorax.

It is also of advantage to thin the edges of the bell slightly to increase its flexibility.

The apparatus is assembled by connecting the suction pump to the shorter tube in the bottle and by connecting the longer tube to the bell by means of rubber tubing. When ready to use the pump is attached to any convenient water faucet and the water turned on. The bell is held for a few seconds against the chest wall covering the thoracotomy incision and drainage tubes (Fig. 254, B). The suction is sufficient to maintain the bell in contact with the chest wall without additional support. It is flexible enough to adapt itself to any surface, adhering closely to either an angular or rounded type chest.

The degree of negative pressure maintained may be regulated by varying the tension of the spring valve in the inlet tube, for whenever the vacuum exceeds the tension at which the spring is set, air will be admitted to the vacuum bottle. If desired the valve may be standardized against a column of mercury. The rapidity of flow of the water through the suction pump may also be used to regulate the degree of negative pressure.

Patients do not complain of pain with judicious application of the apparatus. The use of "Wolff blow bottles" while the apparatus is in place (Fig. 255) is of aid in expanding the lung of the affected side. Pus and retained secretions are very readily evacuated from the chest cavity. Any degree of hyperemia may be produced in the wound by varying the degree of negative pressure. The apparatus is also of advantage in the treatment of other types of suppurating wounds, both because of the hyperemia produced and by the thorough removal of retained secretions. Intermittent irrigation of empyema cavities with Dakin's solution has been employed in all cases in conjunction with the use of this apparatus.

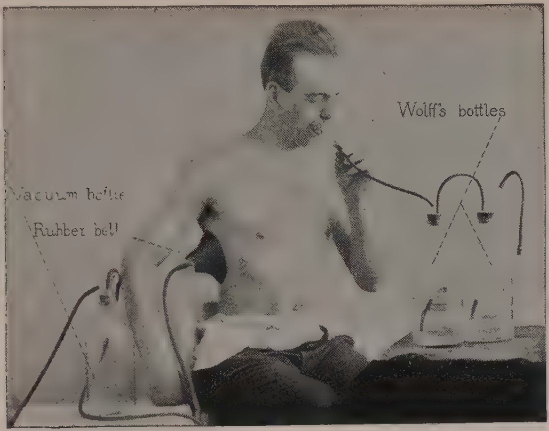

Fig. 255.—Apparatus in use.

A MUSCLE CLAMP TO BE USED IN THYROIDECTOMIES*

EDWARD V. MASTIN

This muscle clamp is particularly serviceable in cases in which the sternohyoid and sternothyroid muscles are cut in the source of thyroidectomy. It has three important features; it does not crush or devitalize the muscle, it does not slip, and the downward curve of the handles prevent them from being in the way of the operator. The weight of the clamp is about that of a 6.5 inch Ochsner clamp, and is constructed so there is $\frac{1}{16}$ inch separation between the jaws when they are closed. The pressure is sufficient to prevent bleeding from the cut edges, yet the muscle is not crushed. The upper jaw is corrugated and contains four pins $\frac{1}{4}$ inch long, which prevent the muscle from slipping. The lower jaw is smooth and thus is easily slipped under the muscle; it contains four holes $\frac{1}{16}$ inch deep, which admit the four pins in the upper jaw.

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* Reprinted from Surgery, Gynecology, and Obstetrics, 1922, xxxv, 644–645. From the Section on Surgery, Mayo Clinic.

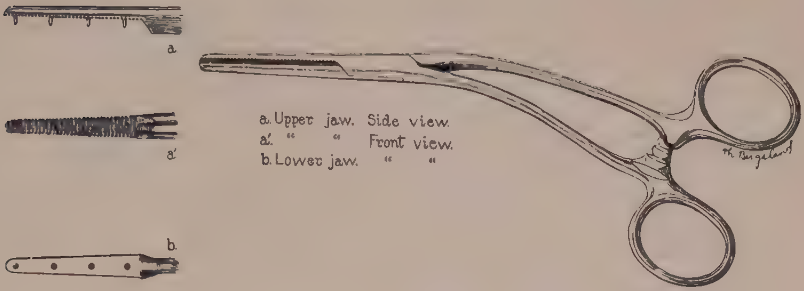

FIG. 256.—Details of the clamp.

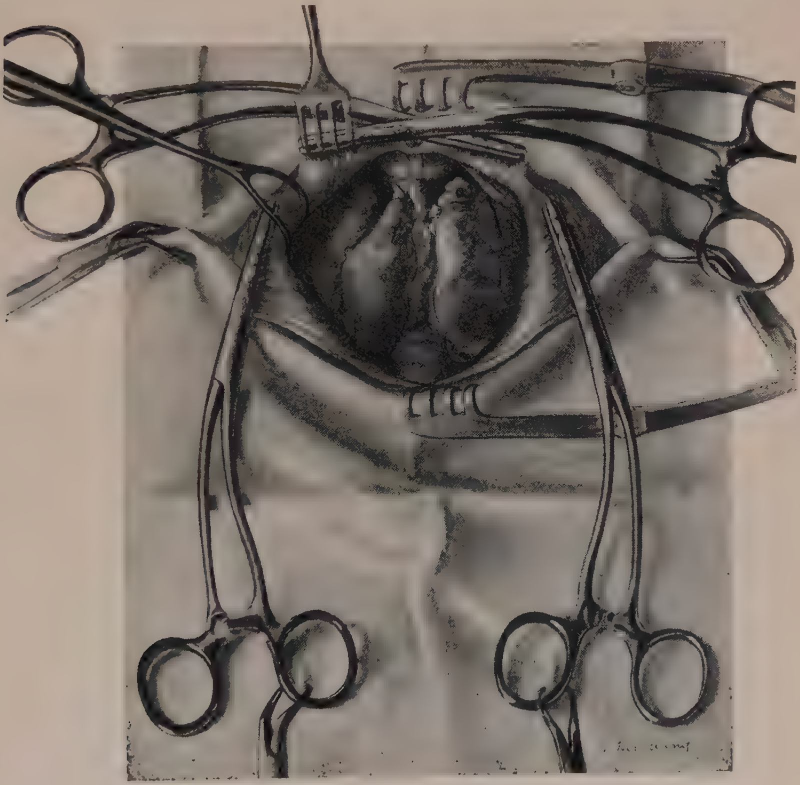

FIG. 257.—Clamp in position.

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